



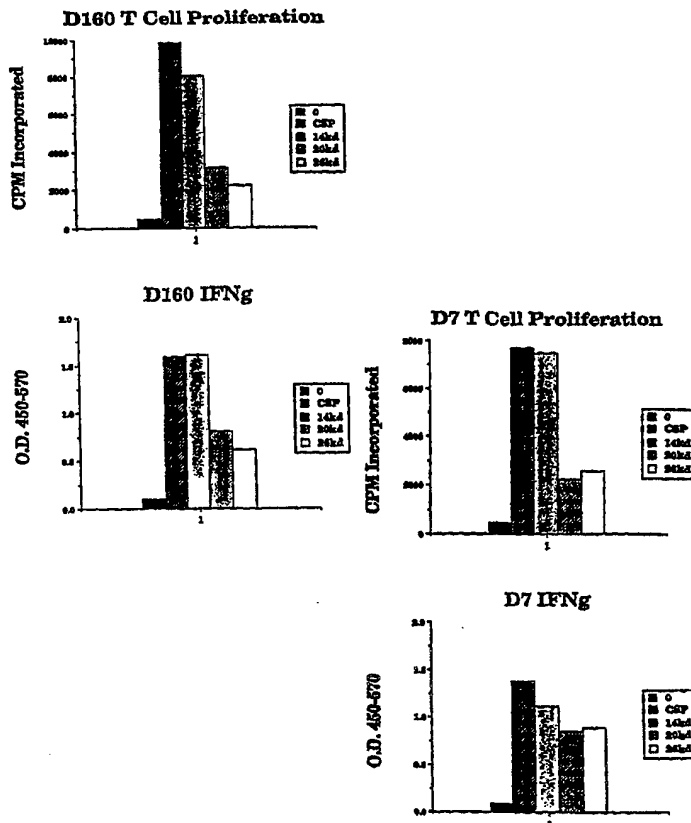
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: COMPOUNDS AND METHODS FOR IMMUNOTHERAPY AND DIAGNOSIS OF TUBERCULOSIS

## (57) Abstract

Compounds and methods for inducing protective immunity against tuberculosis are disclosed. The compounds provided include polypeptides that contain at least one immunogenic portion of one or more *M. tuberculosis* proteins and DNA molecules encoding such polypeptides. Such compounds may be formulated into vaccines and/or pharmaceutical compositions for immunization against *M. tuberculosis* infection, or may be used for the diagnosis of tuberculosis.



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Description5 COMPOUNDS AND METHODS FOR IMMUNOTHERAPY  
AND DIAGNOSIS OF TUBERCULOSISTechnical Field

10 The present invention relates generally to detecting, treating and preventing *Mycobacterium tuberculosis* infection. The invention is more particularly related to polypeptides comprising a *Mycobacterium tuberculosis* antigen, or a portion or other variant thereof, and the use of such polypeptides for diagnosing and vaccinating against *Mycobacterium tuberculosis* infection.

15

Background of the Invention

Tuberculosis is a chronic, infectious disease, that is generally caused by infection with *Mycobacterium tuberculosis*. It is a major disease in developing countries, as well as an increasing problem in developed areas of the world, with about  
20 8 million new cases and 3 million deaths each year. Although the infection may be asymptomatic for a considerable period of time, the disease is most commonly manifested as an acute inflammation of the lungs, resulting in fever and a nonproductive cough. If left untreated, serious complications and death typically result.

Although tuberculosis can generally be controlled using extended  
25 antibiotic therapy, such treatment is not sufficient to prevent the spread of the disease. Infected individuals may be asymptomatic, but contagious, for some time. In addition,

although compliance with the treatment regimen is critical, patient behavior is difficult to monitor. Some patients do not complete the course of treatment, which can lead to ineffective treatment and the development of drug resistance.

Inhibiting the spread of tuberculosis requires effective vaccination and accurate, early diagnosis of the disease. Currently, vaccination with live bacteria is the most efficient method for inducing protective immunity. The most common Mycobacterium employed for this purpose is *Bacillus Calmette-Guerin* (BCG), an avirulent strain of *Mycobacterium bovis*. However, the safety and efficacy of BCG is a source of controversy and some countries, such as the United States, do not vaccinate the general public. Diagnosis is commonly achieved using a skin test, which involves intradermal exposure to tuberculin PPD (protein-purified derivative). Antigen-specific T cell responses result in measurable induration at the injection site by 48-72 hours after injection, which indicates exposure to Mycobacterial antigens. Sensitivity and specificity have, however, been a problem with this test, and individuals vaccinated with BCG cannot be distinguished from infected individuals.

While macrophages have been shown to act as the principal effectors of *M. tuberculosis* immunity, T cells are the predominant inducers of such immunity. The essential role of T cells in protection against *M. tuberculosis* infection is illustrated by the frequent occurrence of *M. tuberculosis* in AIDS patients, due to the depletion of CD4 T cells associated with human immunodeficiency virus (HIV) infection. Mycobacterium-reactive CD4 T cells have been shown to be potent producers of gamma-interferon (IFN- $\gamma$ ), which, in turn, has been shown to trigger the anti-mycobacterial effects of macrophages in mice. While the role of IFN- $\gamma$  in humans is less clear, studies have shown that 1,25-dihydroxy-vitamin D3, either alone or in combination with IFN- $\gamma$  or tumor necrosis factor-alpha, activates human macrophages to inhibit *M. tuberculosis* infection. Furthermore, it is known that IFN- $\gamma$  stimulates human macrophages to make 1,25-dihydroxy-vitamin D3. Similarly, IL-12 has been shown to play a role in stimulating resistance to *M. tuberculosis* infection. For a review of the immunology of *M. tuberculosis* infection see Chan and Kaufmann in

*Tuberculosis: Pathogenesis, Protection and Control*, Bloom (ed.), ASM Press, Washington, DC, 1994.

Accordingly, there is a need in the art for improved vaccines and methods for preventing, treating and detecting tuberculosis. The present invention  
5 fulfills these needs and further provides other related advantages.

#### Summary of the Invention

Briefly stated, this invention provides compounds and methods for preventing and diagnosing tuberculosis. In one aspect, polypeptides are provided  
10 comprising an immunogenic portion of a soluble *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications. In one embodiment of this aspect, the soluble antigen has one of the following N-terminal sequences:

- 15 (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Cys-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu; (SEQ ID No. 120)
- (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser; (SEQ ID No. 121)
- (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg; (SEQ ID No. 122)
- 20 (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro; (SEQ ID No. 123)
- (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val; (SEQ ID No. 124)
- (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro; (SEQ ID  
25 No. 125)
- (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Thr-Ala-Ala-Ser-Pro-Pro-Ser; (SEQ ID No. 126)
- (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-Gly; (SEQ ID No. 127)

- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Leu-Thr-Ser-Leu-Leu-Asn-Ser-Leu-Ala-Asp-Pro-Asn-Val-Ser-Phe-Ala-Asn; (SEQ ID No. 128)
- (j) Xaa-Asp-Ser-Glu-Lys-Ser-Ala-Thr-Ile-Lys-Val-Thr-Asp-Ala-Ser; (SEQ ID No. 134)
- (k) Ala-Gly-Asp-Thr-Xaa-Ile-Tyr-Ile-Val-Gly-Asn-Leu-Thr-Ala-Asp; (SEQ ID No. 135) or
- (l) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 136)

10 wherein Xaa may be any amino acid.

In a related aspect, polypeptides are provided comprising an immunogenic portion of an *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications, the antigen having one of the following N-terminal sequences:

- (m) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No. 137) or
- (n) Asp-Pro-Pro-Asp-Pro-His-Gln-Xaa-Asp-Met-Thr-Lys-Gly-Tyr-Tyr-Pro-Gly-Gly-Arg-Arg-Xaa-Phe; (SEQ ID No. 129)

wherein Xaa may be any amino acid.

20 In another embodiment, the antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos.: 1, 2, 4-10, 13-25, 52, 99 and 101, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 1, 2, 4-10, 13-25, 52, 99 and 101 or a complement thereof under moderately stringent  
25 conditions.

In a related aspect, the polypeptides comprise an immunogenic portion of a *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications, wherein the antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of  
30 the sequences recited in SEQ ID Nos.: 26-51, the complements of said sequences, and

DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 26-51 or a complement thereof under moderately stringent conditions.

In related aspects, DNA sequences encoding the above polypeptides, expression vectors comprising these DNA sequences and host cells transformed or  
5 transfected with such expression vectors are also provided.

In another aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, an inventive polypeptide and a known *M. tuberculosis* antigen.

Within other aspects, the present invention provides pharmaceutical  
10 compositions that comprise one or more of the above polypeptides, or a DNA molecule encoding such polypeptides, and a physiologically acceptable carrier. The invention also provides vaccines comprising one or more of the polypeptides as described above and a non-specific immune response enhancer, together with vaccines comprising one or more DNA sequences encoding such polypeptides and a non-specific immune  
15 response enhancer.

In yet another aspect, methods are provided for inducing protective immunity in a patient, comprising administering to a patient an effective amount of one or more of the above polypeptides.

In further aspects of this invention, methods and diagnostic kits are  
20 provided for detecting tuberculosis in a patient. The methods comprise contacting dermal cells of a patient with one or more of the above polypeptides and detecting an immune response on the patient's skin. The diagnostic kits comprise one or more of the above polypeptides in combination with an apparatus sufficient to contact the polypeptide with the dermal cells of a patient.

25 These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

Brief Description of the Drawings and Sequence Identifiers

Figure 1A and B illustrate the stimulation of proliferation and interferon- $\gamma$  production in T cells derived from a first and a second *M. tuberculosis*-immune donor, respectively, by the 14 Kd, 20 Kd and 26 Kd antigens described in Example 1.

5           Figure 2 illustrates the stimulation of proliferation and interferon- $\gamma$  production in T cells derived from an *M. tuberculosis*-immune individual by the two representative polypeptides TbRa3 and TbRa9.

SEQ. ID NO. 1 is the DNA sequence of TbRa1.  
10       SEQ. ID NO. 2 is the DNA sequence of TbRa10.  
SEQ. ID NO. 3 is the DNA sequence of TbRa11.  
SEQ. ID NO. 4 is the DNA sequence of TbRa12.  
SEQ. ID NO. 5 is the DNA sequence of TbRa13.  
SEQ. ID NO. 6 is the DNA sequence of TbRa16.  
15       SEQ. ID NO. 7 is the DNA sequence of TbRa17.  
SEQ. ID NO. 8 is the DNA sequence of TbRa18.  
SEQ. ID NO. 9 is the DNA sequence of TbRa19.  
SEQ. ID NO. 10 is the DNA sequence of TbRa24.  
SEQ. ID NO. 11 is the DNA sequence of TbRa26.  
20       SEQ. ID NO. 12 is the DNA sequence of TbRa28.  
SEQ. ID NO. 13 is the DNA sequence of TbRa29.  
SEQ. ID NO. 14 is the DNA sequence of TbRa2A.  
SEQ. ID NO. 15 is the DNA sequence of TbRa3.  
SEQ. ID NO. 16 is the DNA sequence of TbRa32.  
25       SEQ. ID NO. 17 is the DNA sequence of TbRa35.  
SEQ. ID NO. 18 is the DNA sequence of TbRa36.  
SEQ. ID NO. 19 is the DNA sequence of TbRa4.  
SEQ. ID NO. 20 is the DNA sequence of TbRa9.  
SEQ. ID NO. 21 is the DNA sequence of TbRaB.  
30       SEQ. ID NO. 22 is the DNA sequence of TbRaC.

SEQ. ID NO. 23 is the DNA sequence of TbRaD.  
SEQ. ID NO. 24 is the DNA sequence of YYWCPG.  
SEQ. ID NO. 25 is the DNA sequence of AAMK.  
SEQ. ID NO. 26 is the DNA sequence of TbL-23.  
5 SEQ. ID NO. 27 is the DNA sequence of TbL-24.  
SEQ. ID NO. 28 is the DNA sequence of TbL-25.  
SEQ. ID NO. 29 is the DNA sequence of TbL-28.  
SEQ. ID NO. 30 is the DNA sequence of TbL-29.  
SEQ. ID NO. 31 is the DNA sequence of TbH-5.  
10 SEQ. ID NO. 32 is the DNA sequence of TbH-8.  
SEQ. ID NO. 33 is the DNA sequence of TbH-9.  
SEQ. ID NO. 34 is the DNA sequence of TbM-1.  
SEQ. ID NO. 35 is the DNA sequence of TbM-3.  
SEQ. ID NO. 36 is the DNA sequence of TbM-6.  
15 SEQ. ID NO. 37 is the DNA sequence of TbM-7.  
SEQ. ID NO. 38 is the DNA sequence of TbM-9.  
SEQ. ID NO. 39 is the DNA sequence of TbM-12.  
SEQ. ID NO. 40 is the DNA sequence of TbM-13.  
SEQ. ID NO. 41 is the DNA sequence of TbM-14.  
20 SEQ. ID NO. 42 is the DNA sequence of TbM-15.  
SEQ. ID NO. 43 is the DNA sequence of TbH-4.  
SEQ. ID NO. 44 is the DNA sequence of TbH-4-FWD.  
SEQ. ID NO. 45 is the DNA sequence of TbH-12.  
SEQ. ID NO. 46 is the DNA sequence of Tb38-1.  
25 SEQ. ID NO. 47 is the DNA sequence of Tb38-4.  
SEQ. ID NO. 48 is the DNA sequence of TbL-17.  
SEQ. ID NO. 49 is the DNA sequence of TbL-20.  
SEQ. ID NO. 50 is the DNA sequence of TbL-21.  
SEQ. ID NO. 51 is the DNA sequence of TbH-16.  
30 SEQ. ID NO. 52 is the DNA sequence of DPEP.

- SEQ. ID NO. 53 is the deduced amino acid sequence of DPEP.
- SEQ. ID NO. 54 is the protein sequence of DPV N-terminal Antigen.
- SEQ. ID NO. 55 is the protein sequence of AVGS N-terminal Antigen.
- SEQ. ID NO. 56 is the protein sequence of AAMK N-terminal Antigen.
- 5 SEQ. ID NO. 57 is the protein sequence of YYWC N-terminal Antigen.
- SEQ. ID NO. 58 is the protein sequence of DIGS N-terminal Antigen.
- SEQ. ID NO. 59 is the protein sequence of AEES N-terminal Antigen.
- SEQ. ID NO. 60 is the protein sequence of DPEP N-terminal Antigen.
- SEQ. ID NO. 61 is the protein sequence of APKT N-terminal Antigen.
- 10 SEQ. ID NO. 62 is the protein sequence of DPAS N-terminal Antigen.
- SEQ. ID NO. 63 is the deduced amino acid sequence of TbRa1.
- SEQ. ID NO. 64 is the deduced amino acid sequence of TbRa10.
- SEQ. ID NO. 65 is the deduced amino acid sequence of TbRa11.
- SEQ. ID NO. 66 is the deduced amino acid sequence of TbRa12.
- 15 SEQ. ID NO. 67 is the deduced amino acid sequence of TbRa13.
- SEQ. ID NO. 68 is the deduced amino acid sequence of TbRa16.
- SEQ. ID NO. 69 is the deduced amino acid sequence of TbRa17.
- SEQ. ID NO. 70 is the deduced amino acid sequence of TbRa18.
- SEQ. ID NO. 71 is the deduced amino acid sequence of TbRa19.
- 20 SEQ. ID NO. 72 is the deduced amino acid sequence of TbRa24.
- SEQ. ID NO. 73 is the deduced amino acid sequence of TbRa26.
- SEQ. ID NO. 74 is the deduced amino acid sequence of TbRa28.
- SEQ. ID NO. 75 is the deduced amino acid sequence of TbRa29.
- SEQ. ID NO. 76 is the deduced amino acid sequence of TbRa2A.
- 25 SEQ. ID NO. 77 is the deduced amino acid sequence of TbRa3.
- SEQ. ID NO. 78 is the deduced amino acid sequence of TbRa32.
- SEQ. ID NO. 79 is the deduced amino acid sequence of TbRa35.
- SEQ. ID NO. 80 is the deduced amino acid sequence of TbRa36.
- SEQ. ID NO. 81 is the deduced amino acid sequence of TbRa4.
- 30 SEQ. ID NO. 82 is the deduced amino acid sequence of TbRa9.

- SEQ. ID NO. 83 is the deduced amino acid sequence of TbRaB.  
SEQ. ID NO. 84 is the deduced amino acid sequence of TbRaC.  
SEQ. ID NO. 85 is the deduced amino acid sequence of TbRaD.  
SEQ. ID NO. 86 is the deduced amino acid sequence of YYWCPG.  
5 SEQ. ID NO. 87 is the deduced amino acid sequence of TbAAMK.  
SEQ. ID NO. 88 is the deduced amino acid sequence of Tb38-1.  
SEQ. ID NO. 89 is the deduced amino acid sequence of TbH-4.  
SEQ. ID NO. 90 is the deduced amino acid sequence of TbH-8.  
SEQ. ID NO. 91 is the deduced amino acid sequence of TbH-9.  
10 SEQ. ID NO. 92 is the deduced amino acid sequence of TbH-12.  
SEQ. ID NO. 93 is the amino acid sequence of Tb38-1 Peptide 1.  
SEQ. ID NO. 94 is the amino acid sequence of Tb38-1 Peptide 2.  
SEQ. ID NO. 95 is the amino acid sequence of Tb38-1 Peptide 3.  
SEQ. ID NO. 96 is the amino acid sequence of Tb38-1 Peptide 4.  
15 SEQ. ID NO. 97 is the amino acid sequence of Tb38-1 Peptide 5.  
SEQ. ID NO. 98 is the amino acid sequence of Tb38-1 Peptide 6.  
SEQ. ID NO. 99 is the DNA sequence of DPAS.  
SEQ. ID NO. 100 is the deduced amino acid sequence of DPAS.  
SEQ. ID NO. 101 is the DNA sequence of DPV.  
20 SEQ. ID NO. 102 is the deduced amino acid sequence of DPV.  
SEQ. ID NO. 103 is the DNA sequence of ESAT-6.  
SEQ. ID NO. 104 is the deduced amino acid sequence of ESAT-6.  
SEQ. ID NO. 105 is the DNA sequence of TbH-8-2.  
SEQ. ID NO. 106 is the DNA sequence of TbH-9FL.  
25 SEQ. ID NO. 107 is the deduced amino acid sequence of TbH-9FL.  
SEQ. ID NO. 108 is the DNA sequence of TbH-9-1.  
SEQ. ID NO. 109 is the deduced amino acid sequence of TbH-9-1.  
SEQ. ID NO. 110 is the DNA sequence of TbH-9-4.  
SEQ. ID NO. 111 is the deduced amino acid sequence of TbH-9-4.  
30 SEQ. ID NO. 112 is the DNA sequence of Tb38-1F2 IN.

SEQ. ID NO. 113 is the DNA sequence of Tb38-2F2 RP.

SEQ. ID NO. 114 is the deduced amino acid sequence of Tb37-FL.

SEQ. ID NO. 115 is the deduced amino acid sequence of Tb38-IN.

SEQ. ID NO. 116 is the DNA sequence of Tb38-1F3.

5 SEQ. ID NO. 117 is the deduced amino acid sequence of Tb38-1F3.

SEQ. ID NO. 118 is the DNA sequence of Tb38-1F5.

SEQ. ID NO. 119 is the DNA sequence of Tb38-1F6.

SEQ. ID NO. 120 is the deduced N-terminal amino acid sequence of DPV.

SEQ. ID NO. 121 is the deduced N-terminal amino acid sequence of AVGS.

10 SEQ. ID NO. 122 is the deduced N-terminal amino acid sequence of AAMK.

SEQ. ID NO. 123 is the deduced N-terminal amino acid sequence of YYWC.

SEQ. ID NO. 124 is the deduced N-terminal amino acid sequence of DIGS.

SEQ. ID NO. 125 is the deduced N-terminal amino acid sequence of AEES.

SEQ. ID NO. 126 is the deduced N-terminal amino acid sequence of DPEP.

15 SEQ. ID NO. 127 is the deduced N-terminal amino acid sequence of APKT.

SEQ. ID NO. 128 is the deduced amino acid sequence of DPAS.

SEQ. ID NO. 129 is the protein sequence of DPPD N-terminal Antigen.

SEQ ID NO. 130-133 are the protein sequences of four DPPD cyanogen bromide fragments.

20 SEQ ID NO. 134 is the N-terminal protein sequence of XDS antigen.

SEQ ID NO. 135 is the N-terminal protein sequence of AGD antigen.

SEQ ID NO. 136 is the N-terminal protein sequence of APE antigen.

SEQ ID NO. 137 is the N-terminal protein sequence of XYI antigen.

## 25 Detailed Description of the Invention

As noted above, the present invention is generally directed to compositions and methods for preventing, treating and diagnosing tuberculosis. The compositions of the subject invention include polypeptides that comprise at least one immunogenic portion of a *M. tuberculosis* antigen, or a variant of such an antigen that  
30 differs only in conservative substitutions and/or modifications. Polypeptides within the scope of the present invention include, but are not limited to, immunogenic soluble

*M. tuberculosis* antigens. A "soluble *M. tuberculosis* antigen" is a protein of *M. tuberculosis* origin that is present in *M. tuberculosis* culture filtrate. As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full length proteins (*i.e.*, antigens), wherein the amino acid residues are linked by covalent peptide bonds. Thus, a polypeptide comprising an immunogenic portion of one of the above antigens may consist entirely of the immunogenic portion, or may contain additional sequences. The additional sequences may be derived from the native *M. tuberculosis* antigen or may be heterologous, and such sequences may (but need not) be immunogenic.

"Immunogenic," as used herein, refers to the ability to elicit an immune response (*e.g.*, cellular) in a patient, such as a human, and/or in a biological sample. In particular, antigens that are immunogenic (and immunogenic portions or other variants of such antigens) are capable of stimulating cell proliferation, interleukin-12 production and/or interferon- $\gamma$  production in biological samples comprising one or more cells selected from the group of T cells, NK cells, B cells and macrophages, where the cells are derived from an *M. tuberculosis*-immune individual. Polypeptides comprising at least an immunogenic portion of one or more *M. tuberculosis* antigens may generally be used to detect tuberculosis or to induce protective immunity against tuberculosis in a patient.

The compositions and methods of this invention also encompass variants of the above polypeptides. A "variant," as used herein, is a polypeptide that differs from the native antigen only in conservative substitutions and/or modifications, such that the ability of the polypeptide to induce an immune response is retained. Such variants may generally be identified by modifying one of the above polypeptide sequences, and evaluating the immunogenic properties of the modified polypeptide using, for example, the representative procedures described herein.

A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. In general, the following

groups of amino acids represent conservative changes: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

5 Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenic properties, secondary structure and hydrophobic nature of the polypeptide. For example, a polypeptide may be conjugated to a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease  
10 of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

In a related aspect, combination polypeptides are disclosed. A "combination polypeptide" is a polypeptide comprising at least one of the above  
15 immunogenic portions and one or more additional immunogenic *M. tuberculosis* sequences, which are joined via a peptide linkage into a single amino acid chain. The sequences may be joined directly (i.e., with no intervening amino acids) or may be joined by way of a linker sequence (e.g., Gly-Cys-Gly) that does not significantly diminish the immunogenic properties of the component polypeptides.

20 In general, *M. tuberculosis* antigens, and DNA sequences encoding such antigens, may be prepared using any of a variety of procedures. For example, soluble antigens may be isolated from *M. tuberculosis* culture filtrate by procedures known to those of ordinary skill in the art, including anion-exchange and reverse phase chromatography. Purified antigens are then evaluated for their ability to elicit an  
25 appropriate immune response (e.g., cellular) using, for example, the representative methods described herein. Immunogenic antigens may then be partially sequenced using techniques such as traditional Edman chemistry. See Edman and Berg, *Eur. J. Biochem.* 80:116-132, 1967.

Immunogenic antigens may also be produced recombinantly using a  
30 DNA sequence that encodes the antigen, which has been inserted into an expression

vector and expressed in an appropriate host. DNA molecules encoding soluble antigens may be isolated by screening an appropriate *M. tuberculosis* expression library with anti-sera (e.g., rabbit) raised specifically against soluble *M. tuberculosis* antigens. DNA sequences encoding antigens that may or may not be soluble may be identified by  
5 screening an appropriate *M. tuberculosis* genomic or cDNA expression library with sera obtained from patients infected with *M. tuberculosis*. Such screens may generally be performed using techniques well known to those of ordinary skill in the art, such as those described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989.

10 DNA sequences encoding soluble antigens may also be obtained by screening an appropriate *M. tuberculosis* cDNA or genomic DNA library for DNA sequences that hybridize to degenerate oligonucleotides derived from partial amino acid sequences of isolated soluble antigens. Degenerate oligonucleotide sequences for use in such a screen may be designed and synthesized, and the screen may be performed, as  
15 described (for example) in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989 (and references cited therein). Polymerase chain reaction (PCR) may also be employed, using the above oligonucleotides in methods well known in the art, to isolate a nucleic acid probe from a cDNA or genomic library. The library screen may then be performed using the isolated  
20 probe.

Alternatively, genomic or cDNA libraries derived from *M. tuberculosis* may be screened directly using peripheral blood mononuclear cells (PBMCs) or T cell lines or clones derived from one or more *M. tuberculosis*-immune individuals. In general, PBMCs and/or T cells for use in such screens may be prepared as described  
25 below. Direct library screens may generally be performed by assaying pools of expressed recombinant proteins for the ability to induce proliferation and/or interferon- $\gamma$  production in T cells derived from an *M. tuberculosis*-immune individual. Alternatively, potential T cell antigens may be first selected based on antibody reactivity, as described above.

Regardless of the method of preparation, the antigens (and immunogenic portions thereof) described herein (which may or may not be soluble) have the ability to induce an immunogenic response. More specifically, the antigens have the ability to induce proliferation and/or cytokine production (*i.e.*, interferon- $\gamma$  and/or interleukin-12 production) in T cells, NK cells, B cells and/or macrophages derived from an *M. tuberculosis*-immune individual. The selection of cell type for use in evaluating an immunogenic response to a antigen will, of course, depend on the desired response. For example, interleukin-12 production is most readily evaluated using preparations containing B cells and/or macrophages. An *M. tuberculosis*-immune individual is one who is considered to be resistant to the development of tuberculosis by virtue of having mounted an effective T cell response to *M. tuberculosis* (*i.e.*, substantially free of disease symptoms). Such individuals may be identified based on a strongly positive (*i.e.*, greater than about 10 mm diameter induration) intradermal skin test response to tuberculosis proteins (PPD) and an absence of any signs or symptoms of tuberculosis disease. T cells, NK cells, B cells and macrophages derived from *M. tuberculosis*-immune individuals may be prepared using methods known to those of ordinary skill in the art. For example, a preparation of PBMCs (*i.e.*, peripheral blood mononuclear cells) may be employed without further separation of component cells. PBMCs may generally be prepared, for example, using density centrifugation through Ficoll™ (Winthrop Laboratories, NY). T cells for use in the assays described herein may also be purified directly from PBMCs. Alternatively, an enriched T cell line reactive against mycobacterial proteins, or T cell clones reactive to individual mycobacterial proteins, may be employed. Such T cell clones may be generated by, for example, culturing PBMCs from *M. tuberculosis*-immune individuals with mycobacterial proteins for a period of 2-4 weeks. This allows expansion of only the mycobacterial protein-specific T cells, resulting in a line composed solely of such cells. These cells may then be cloned and tested with individual proteins, using methods known to those of ordinary skill in the art, to more accurately define individual T cell specificity. In general, antigens that test positive in assays for proliferation and/or cytokine production (*i.e.*, interferon- $\gamma$  and/or interleukin-12 production) performed using T cells, NK cells, B cells

and/or macrophages derived from an *M. tuberculosis*-immune individual are considered immunogenic. Such assays may be performed, for example, using the representative procedures described below. Immunogenic portions of such antigens may be identified using similar assays, and may be present within the polypeptides described herein.

5           The ability of a polypeptide (*e.g.*, an immunogenic antigen, or a portion or other variant thereof) to induce cell proliferation is evaluated by contacting the cells (*e.g.*, T cells and/or NK cells) with the polypeptide and measuring the proliferation of the cells. In general, the amount of polypeptide that is sufficient for evaluation of about  $10^5$  cells ranges from about 10 ng/mL to about 100  $\mu$ g/mL and preferably is about  
10   10  $\mu$ g/mL. The incubation of polypeptide with cells is typically performed at 37°C for about six days. Following incubation with polypeptide, the cells are assayed for a proliferative response, which may be evaluated by methods known to those of ordinary skill in the art, such as exposing cells to a pulse of radiolabeled thymidine and measuring the incorporation of label into cellular DNA. In general, a polypeptide that  
15   results in at least a three fold increase in proliferation above background (*i.e.*, the proliferation observed for cells cultured without polypeptide) is considered to be able to induce proliferation.

          The ability of a polypeptide to stimulate the production of interferon- $\gamma$  and/or interleukin-12 in cells may be evaluated by contacting the cells with the  
20   polypeptide and measuring the level of interferon- $\gamma$  or interleukin-12 produced by the cells. In general, the amount of polypeptide that is sufficient for the evaluation of about  $10^5$  cells ranges from about 10 ng/mL to about 100  $\mu$ g/mL and preferably is about 10  $\mu$ g/mL. The polypeptide may, but need not, be immobilized on a solid support, such as a bead or a biodegradable microsphere, such as those described in U.S. Patent  
25   Nos. 4,897,268 and 5,075,109. The incubation of polypeptide with the cells is typically performed at 37°C for about six days. Following incubation with polypeptide, the cells are assayed for interferon- $\gamma$  and/or interleukin-12 (or one or more subunits thereof), which may be evaluated by methods known to those of ordinary skill in the art, such as an enzyme-linked immunosorbent assay (ELISA) or, in the case of IL-12 P70 subunit, a  
30   bioassay such as an assay measuring proliferation of T cells. In general, a polypeptide

that results in the production of at least 50 pg of interferon- $\gamma$  per mL of cultured supernatant (containing  $10^4$ - $10^5$  T cells per mL) is considered able to stimulate the production of interferon- $\gamma$ . A polypeptide that stimulates the production of at least 10 pg/mL of IL-12 P70 subunit, and/or at least 100 pg/mL of IL-12 P40 subunit, per  $10^5$  macrophages or B cells (or per  $3 \times 10^5$  PBMC) is considered able to stimulate the production of IL-12.

In general, immunogenic antigens are those antigens that stimulate proliferation and/or cytokine production (*i.e.*, interferon- $\gamma$  and/or interleukin-12 production) in T cells, NK cells, B cells and/or macrophages derived from at least about 25% of *M. tuberculosis*-immune individuals. Among these immunogenic antigens, polypeptides having superior therapeutic properties may be distinguished based on the magnitude of the responses in the above assays and based on the percentage of individuals for which a response is observed. In addition, antigens having superior therapeutic properties will not stimulate proliferation and/or cytokine production *in vitro* in cells derived from more than about 25% of individuals that are not *M. tuberculosis*-immune, thereby eliminating responses that are not specifically due to *M. tuberculosis*-responsive cells. Those antigens that induce a response in a high percentage of T cell, NK cell, B cell and/or macrophage preparations from *M. tuberculosis*-immune individuals (with a low incidence of responses in cell preparations from other individuals) have superior therapeutic properties.

Antigens with superior therapeutic properties may also be identified based on their ability to diminish the severity of *M. tuberculosis* infection in experimental animals, when administered as a vaccine. Suitable vaccine preparations for use on experimental animals are described in detail below. Efficacy may be determined based on the ability of the antigen to provide at least about a 50% reduction in bacterial numbers and/or at least about a 40% decrease in mortality following experimental infection. Suitable experimental animals include mice, guinea pigs and primates.

Antigens having superior diagnostic properties may generally be identified based on the ability to elicit a response in an intradermal skin test performed

on an individual with active tuberculosis, but not in a test performed on an individual who is not infected with *M. tuberculosis*. Skin tests may generally be performed as described below, with a response of at least 5 mm induration considered positive.

Immunogenic portions of the antigens described herein may be prepared  
5 and identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3d ed., Raven Press, 1993, pp. 243-247 and references cited therein. Such techniques include screening polypeptide portions of the native antigen for immunogenic properties. The representative proliferation and cytokine production assays described herein may generally be employed in these screens. An immunogenic  
10 portion of a polypeptide is a portion that, within such representative assays, generates an immune response (*e.g.*, proliferation, interferon- $\gamma$  production and/or interleukin-12 production) that is substantially similar to that generated by the full length antigen. In other words, an immunogenic portion of an antigen may generate at least about 20%, and preferably about 100%, of the proliferation induced by the full length antigen in the  
15 model proliferation assay described herein. An immunogenic portion may also, or alternatively, stimulate the production of at least about 20%, and preferably about 100%, of the interferon- $\gamma$  and/or interleukin-12 induced by the full length antigen in the model assay described herein.

Portions and other variants of *M. tuberculosis* antigens may be generated  
20 by synthetic or recombinant means. Synthetic polypeptides having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are  
25 sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Applied BioSystems, Inc., Foster City, CA, and may be operated according to the manufacturer's instructions. Variants of a native antigen may generally be prepared using standard mutagenesis techniques, such  
30 as oligonucleotide-directed site-specific mutagenesis. Sections of the DNA sequence

may also be removed using standard techniques to permit preparation of truncated polypeptides.

Recombinant polypeptides containing portions and/or variants of a native antigen may be readily prepared from a DNA sequence encoding the polypeptide using a variety of techniques well known to those of ordinary skill in the art. For example, supernatants from suitable host/vector systems which secrete recombinant protein into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant protein.

Any of a variety of expression vectors known to those of ordinary skill in the art may be employed to express recombinant polypeptides of this invention. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. The DNA sequences expressed in this manner may encode naturally occurring antigens, portions of naturally occurring antigens, or other variants thereof.

In general, regardless of the method of preparation, the polypeptides disclosed herein are prepared in substantially pure form. Preferably, the polypeptides are at least about 80% pure, more preferably at least about 90% pure and most preferably at least about 99% pure. In certain preferred embodiments, described in detail below, the substantially pure polypeptides are incorporated into pharmaceutical compositions or vaccines for use in one or more of the methods disclosed herein.

In certain specific embodiments, the subject invention discloses polypeptides comprising at least an immunogenic portion of a soluble *M. tuberculosis* antigen having one of the following N-terminal sequences, or a variant thereof that differs only in conservative substitutions and/or modifications:

- 5 (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Cys-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu; (SEQ ID No. 120)
- (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser; (SEQ ID No. 121)
- (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg; (SEQ ID No. 122)
- (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro; (SEQ ID No. 123)
- 10 (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val; (SEQ ID No. 124)
- (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro; (SEQ ID No. 125)
- (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Ala-Ala-Ala-Ser-Pro-Pro-Ser; (SEQ ID No. 126)
- 15 (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-Gly; (SEQ ID No. 127)
- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Leu-Thr-Ser-Leu-Leu-Asn-Ser-Leu-Ala-Asp-Pro-Asn-Val-Ser-Phe-Ala-Asn; (SEQ ID No. 128)
- 20 (j) Xaa-Asp-Ser-Glu-Lys-Ser-Ala-Thr-Ile-Lys-Val-Thr-Asp-Ala-Ser; (SEQ ID No. 134)
- (k) Ala-Gly-Asp-Thr-Xaa-Ile-Tyr-Ile-Val-Gly-Asn-Leu-Thr-Ala-Asp; (SEQ ID No. 135) or
- (l) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 136)
- 25

wherein Xaa may be any amino acid, preferably a cysteine residue. A DNA sequence encoding the antigen identified as (g) above is provided in SEQ ID No. 52, and the polypeptide encoded by SEQ ID No. 52 is provided in SEQ ID No. 53. A DNA sequence encoding the antigen defined as (a) above is provided in SEQ ID No. 101; its deduced amino acid sequence is provided in SEQ ID No. 102. A DNA sequence

30

corresponding to antigen (d) above is provided in SEQ ID No. 24 a DNA sequence corresponding to antigen (c) is provided in SEQ ID No. 25 and a DNA sequence corresponding to antigen (i) is provided in SEQ ID No. 99; its deduced amino acid sequence is provided in SEQ ID No. 100.

5 In a further specific embodiment, the subject invention discloses polypeptides comprising at least an immunogenic portion of an *M. tuberculosis* antigen having one of the following N-terminal sequences, or a variant thereof that differs only in conservative substitutions and/or modifications:

- 10 (m) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No 137) or
- (n) Asp-Pro-Pro-Asp-Pro-His-Gln-Xaa-Asp-Met-Thr-Lys-Gly-Tyr-Tyr-Pro-Gly-Gly-Arg-Arg-Xaa-Phe; (SEQ ID No. 129)

wherein Xaa may be any amino acid, preferably a cysteine residue.

15 In other specific embodiments, the subject invention discloses polypeptides comprising at least an immunogenic portion of a soluble *M. tuberculosis* antigen (or a variant of such an antigen) that comprises one or more of the amino acid sequences encoded by (a) the DNA sequences of SEQ ID Nos.: 1, 2, 4-10, 13-25 and 52; (b) the complements of such DNA sequences, or (c) DNA sequences substantially homologous to a sequence in (a) or (b).

20 In further specific embodiments, the subject invention discloses polypeptides comprising at least an immunogenic portion of a *M. tuberculosis* antigen (or a variant of such an antigen), which may or may not be soluble, that comprises one or more of the amino acid sequences encoded by (a) the DNA sequences of SEQ ID Nos.: 26-51, (b) the complements of such DNA sequences or (c) DNA sequences

25 substantially homologous to a sequence in (a) or (b).

In the specific embodiments discussed above, the *M. tuberculosis* antigens include variants that are encoded by DNA sequences which are substantially homologous to one or more of DNA sequences specifically recited herein. "Substantial homology," as used herein, refers to DNA sequences that are capable of hybridizing

30 under moderately stringent conditions. Suitable moderately stringent conditions include

prewashing in a solution of 5X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5X SSC, overnight or, in the case of cross-species homology at 45°C, 0.5X SSC; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS). Such hybridizing DNA sequences are also  
5 within the scope of this invention, as are nucleotide sequences that, due to code degeneracy, encode an immunogenic polypeptide that is encoded by a hybridizing DNA sequence.

In a related aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, a polypeptide of  
10 the present invention and a known *M tuberculosis* antigen, such as the 38 kD antigen described above or ESAT-6 (SEQ ID Nos. 103 and 104), together with variants of such fusion proteins. The fusion proteins of the present invention may also include a linker peptide between the first and second polypeptides.

A DNA sequence encoding a fusion protein of the present invention is  
15 constructed using known recombinant DNA techniques to assemble separate DNA sequences encoding the first and second polypeptides into an appropriate expression vector. The 3' end of a DNA sequence encoding the first polypeptide is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide so that the reading frames of the sequences are in phase to permit mRNA  
20 translation of the two DNA sequences into a single fusion protein that retains the biological activity of both the first and the second polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptides by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into  
25 the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide  
30 functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser

residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene* 40:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent  
5 No. 4,751,180. The linker sequence may be from 1 to about 50 amino acids in length. Peptide sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable  
10 transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons require to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

15 In another aspect, the present invention provides methods for using one or more of the above polypeptides or fusion proteins (or DNA molecules encoding such polypeptides) to induce protective immunity against tuberculosis in a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may be afflicted with a disease, or may be free of detectable disease and/or infection. In  
20 other words, protective immunity may be induced to prevent or treat tuberculosis.

In this aspect, the polypeptide, fusion protein or DNA molecule is generally present within a pharmaceutical composition and/or a vaccine. Pharmaceutical compositions may comprise one or more polypeptides, each of which may contain one or more of the above sequences (or variants thereof), and a  
25 physiologically acceptable carrier. Vaccines may comprise one or more of the above polypeptides and a non-specific immune response enhancer, such as an adjuvant or a liposome (into which the polypeptide is incorporated). Such pharmaceutical compositions and vaccines may also contain other *M. tuberculosis* antigens, either incorporated into a combination polypeptide or present within a separate polypeptide.

Alternatively, a vaccine may contain DNA encoding one or more polypeptides as described above, such that the polypeptide is generated *in situ*. In such vaccines, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacterial and viral expression systems. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface. In a preferred embodiment, the DNA may be introduced using a viral expression system (*e.g.*, vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

In a related aspect, a DNA vaccine as described above may be administered simultaneously with or sequentially to either a polypeptide of the present invention or a known *M. tuberculosis* antigen, such as the 38 kD antigen described above. For example, administration of DNA encoding a polypeptide of the present invention, either "naked" or in a delivery system as described above, may be followed by administration of an antigen in order to enhance the protective immune effect of the vaccine.

Routes and frequency of administration, as well as dosage, will vary from individual to individual and may parallel those currently being used in immunization using BCG. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Between 1 and 3 doses may be administered for a 1-36 week period. Preferably, 3 doses are administered, at

intervals of 3-4 months, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of polypeptide or DNA that, when administered as described above, is capable of raising an immune response in an immunized patient sufficient to protect the patient  
5 from *M. tuberculosis* infection for at least 1-2 years. In general, the amount of polypeptide present in a dose (or produced *in situ* by the DNA in a dose) ranges from about 1 pg to about 100 mg per kg of host, typically from about 10 pg to about 1 mg, and preferably from about 100 pg to about 1  $\mu$ g. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

10 While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier,  
15 such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactic galactide) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

20 Any of a variety of adjuvants may be employed in the vaccines of this invention to nonspecifically enhance the immune response. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a nonspecific stimulator of immune responses, such as lipid A, *Bordetella pertussis* or *Mycobacterium tuberculosis*. Suitable adjuvants are  
25 commercially available as, for example, Freund's Incomplete Adjuvant and Freund's Complete Adjuvant (Difco Laboratories) and Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ). Other suitable adjuvants include alum, biodegradable microspheres, monophosphoryl lipid A and quil A.

30 In another aspect, this invention provides methods for using one or more of the polypeptides described above to diagnose tuberculosis using a skin test. As used

herein, a "skin test" is any assay performed directly on a patient in which a delayed-type hypersensitivity (DTH) reaction (such as swelling, reddening or dermatitis) is measured following intradermal injection of one or more polypeptides as described above. Such injection may be achieved using any suitable device sufficient to contact the polypeptide or polypeptides with dermal cells of the patient, such as a tuberculin syringe or 1 mL syringe. Preferably, the reaction is measured at least 48 hours after injection, more preferably 48-72 hours.

The DTH reaction is a cell-mediated immune response, which is greater in patients that have been exposed previously to the test antigen (*i.e.*, the immunogenic portion of the polypeptide employed, or a variant thereof). The response may be measured visually, using a ruler. In general, a response that is greater than about 0.5 cm in diameter, preferably greater than about 1.0 cm in diameter, is a positive response, indicative of tuberculosis infection, which may or may not be manifested as an active disease.

The polypeptides of this invention are preferably formulated, for use in a skin test, as pharmaceutical compositions containing a polypeptide and a physiologically acceptable carrier, as described above. Such compositions typically contain one or more of the above polypeptides in an amount ranging from about 1  $\mu$ g to about 100  $\mu$ g, preferably from about 10  $\mu$ g to about 50  $\mu$ g in a volume of 0.1 mL. Preferably, the carrier employed in such pharmaceutical compositions is a saline solution with appropriate preservatives, such as phenol and/or Tween 80™.

In a preferred embodiment, a polypeptide employed in a skin test is of sufficient size such that it remains at the site of injection for the duration of the reaction period. In general, a polypeptide that is at least 9 amino acids in length is sufficient. The polypeptide is also preferably broken down by macrophages within hours of injection to allow presentation to T-cells. Such polypeptides may contain repeats of one or more of the above sequences and/or other immunogenic or nonimmunogenic sequences.

The following Examples are offered by way of illustration and not by way of limitation.

## EXAMPLES

5

### EXAMPLE 1

#### PURIFICATION AND CHARACTERIZATION OF POLYPEPTIDES

##### FROM *M. TUBERCULOSIS* CULTURE FILTRATE

10 This example illustrates the preparation of *M. tuberculosis* soluble polypeptides from culture filtrate. Unless otherwise noted, all percentages in the following example are weight per volume.

*M. tuberculosis* (either H37Ra, ATCC No. 25177, or H37Rv, ATCC No. 25618) was cultured in sterile GAS media at 37°C for fourteen days. The media  
15 was then vacuum filtered (leaving the bulk of the cells) through a 0.45 µ filter into a sterile 2.5 L bottle. The media was next filtered through a 0.2 µ filter into a sterile 4 L bottle and NaN<sub>3</sub> was added to the culture filtrate to a concentration of 0.04%. The bottles were then placed in a 4°C cold room.

The culture filtrate was concentrated by placing the filtrate in a 12 L  
20 reservoir that had been autoclaved and feeding the filtrate into a 400 ml Amicon stir cell which had been rinsed with ethanol and contained a 10,000 kDa MWCO membrane. The pressure was maintained at 60 psi using nitrogen gas. This procedure reduced the 12 L volume to approximately 50 ml.

The culture filtrate was dialyzed into 0.1% ammonium bicarbonate using  
25 a 8,000 kDa MWCO cellulose ester membrane, with two changes of ammonium bicarbonate solution. Protein concentration was then determined by a commercially available BCA assay (Pierce, Rockford, IL).

The dialyzed culture filtrate was then lyophilized, and the polypeptides resuspended in distilled water. The polypeptides were dialyzed against 0.01 mM 1,3  
30 bis[tris(hydroxymethyl)-methylamino]propane, pH 7.5 (Bis-Tris propane buffer), the

initial conditions for anion exchange chromatography. Fractionation was performed using gel perfusion chromatography on a POROS 146 II Q/M anion exchange column 4.6 mm x 100 mm (Perseptive BioSystems, Framingham, MA) equilibrated in 0.01 mM Bis-Tris propane buffer pH 7.5. Polypeptides were eluted with a linear 0-0.5 M NaCl  
5 gradient in the above buffer system. The column eluent was monitored at a wavelength of 220 nm.

The pools of polypeptides eluting from the ion exchange column were dialyzed against distilled water and lyophilized. The resulting material was dissolved in 0.1% trifluoroacetic acid (TFA) pH 1.9 in water, and the polypeptides were purified on  
10 a Delta-Pak C18 column (Waters, Milford, MA) 300 Angstrom pore size, 5 micron particle size (3.9 x 150 mm). The polypeptides were eluted from the column with a linear gradient from 0-60% dilution buffer (0.1% TFA in acetonitrile). The flow rate was 0.75 ml/minute and the HPLC eluent was monitored at 214 nm. Fractions containing the eluted polypeptides were collected to maximize the purity of the  
15 individual samples. Approximately 200 purified polypeptides were obtained.

The purified polypeptides were then screened for the ability to induce T-cell proliferation in PBMC preparations. The PBMCs from donors known to be PPD skin test positive and whose T-cells were shown to proliferate in response to PPD and crude soluble proteins from MTB were cultured in medium comprising RPMI 1640  
20 supplemented with 10% pooled human serum and 50 µg/ml gentamicin. Purified polypeptides were added in duplicate at concentrations of 0.5 to 10 µg/mL. After six days of culture in 96-well round-bottom plates in a volume of 200 µl, 50 µl of medium was removed from each well for determination of IFN-γ levels, as described below. The plates were then pulsed with 1 µCi/well of tritiated thymidine for a further 18  
25 hours, harvested and tritium uptake determined using a gas scintillation counter. Fractions that resulted in proliferation in both replicates three fold greater than the proliferation observed in cells cultured in medium alone were considered positive.

IFN-γ was measured using an enzyme-linked immunosorbent assay (ELISA). ELISA plates were coated with a mouse monoclonal antibody directed to  
30 human IFN-γ (PharMingen, San Diego, CA) in PBS for four hours at room temperature.

Wells were then blocked with PBS containing 5% (W/V) non-fat dried milk for 1 hour at room temperature. The plates were then washed six times in PBS/0.2% TWEEN-20 and samples diluted 1:2 in culture medium in the ELISA plates were incubated overnight at room temperature. The plates were again washed and a polyclonal rabbit  
5 anti-human IFN- $\gamma$  serum diluted 1:3000 in PBS/10% normal goat serum was added to each well. The plates were then incubated for two hours at room temperature, washed and horseradish peroxidase-coupled anti-rabbit IgG (Sigma Chemical So., St. Louis, MO) was added at a 1:2000 dilution in PBS/5% non-fat dried milk. After a further two hour incubation at room temperature, the plates were washed and TMB substrate added.  
10 The reaction was stopped after 20 min with 1 N sulfuric acid. Optical density was determined at 450 nm using 570 nm as a reference wavelength. Fractions that resulted in both replicates giving an OD two fold greater than the mean OD from cells cultured in medium alone, plus 3 standard deviations, were considered positive.

For sequencing, the polypeptides were individually dried onto  
15 Biobrene™ (Perkin Elmer/Applied BioSystems Division, Foster City, CA) treated glass fiber filters. The filters with polypeptide were loaded onto a Perkin Elmer/Applied BioSystems Division Procise 492 protein sequencer. The polypeptides were sequenced from the amino terminal and using traditional Edman chemistry. The amino acid sequence was determined for each polypeptide by comparing the retention time of the  
20 PTH amino acid derivative to the appropriate PTH derivative standards.

Using the procedure described above, antigens having the following N-terminal sequences were isolated:

- (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Xaa-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu; (SEQ ID No. 54)
- 25 (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser; (SEQ ID No. 55)
- (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg; (SEQ ID No. 56)
- (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro; (SEQ ID No. 57)  
30

- (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val;  
(SEQ ID No. 58)
- (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro; (SEQ ID  
No. 59)
- 5 (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Ala-Ala-Ala-Ala-  
Pro-Pro-Ala; (SEQ ID No. 60) and
- (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-  
Gly; (SEQ ID No. 61)

wherein Xaa may be any amino acid.

10 An additional antigen was isolated employing a microbore HPLC  
purification step in addition to the procedure described above. Specifically, 20 µl of a  
fraction comprising a mixture of antigens from the chromatographic purification step  
previously described, was purified on an Aquapore C18 column (Perkin Elmer/Applied  
Biosystems Division, Foster City, CA) with a 7 micron pore size, column size 1 mm x  
15 100 mm, in a Perkin Elmer/Applied Biosystems Division Model 172 HPLC. Fractions  
were eluted from the column with a linear gradient of 1%/minute of acetonitrile  
(containing 0.05% TFA) in water (0.05% TFA) at a flow rate of 80 µl/minute. The  
eluent was monitored at 250 nm. The original fraction was separated into 4 major peaks  
plus other smaller components and a polypeptide was obtained which was shown to  
20 have a molecular weight of 12.054 Kd (by mass spectrometry) and the following N-  
terminal sequence:

- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Gln-  
Thr-Ser-Leu-Leu-Asn-Asn-Leu-Ala-Asp-Pro-Asp-Val-Ser-Phe-  
Ala-Asp (SEQ ID No. 62).

25 This polypeptide was shown to induce proliferation and IFN-γ production in PBMC  
preparations using the assays described above.

Additional soluble antigens were isolated from *M. tuberculosis* culture  
filtrate as follows. *M. tuberculosis* culture filtrate was prepared as described above.  
Following dialysis against Bis-Tris propane buffer, at pH 5.5, fractionation was  
30 performed using anion exchange chromatography on a Poros QE column 4.6 x 100 mm

(Perseptive Biosystems) equilibrated in Bis-Tris propane buffer pH 5.5. Polypeptides were eluted with a linear 0-1.5 M NaCl gradient in the above buffer system at a flow rate of 10 ml/min. The column eluent was monitored at a wavelength of 214 nm.

The fractions eluting from the ion exchange column were pooled and  
5 subjected to reverse phase chromatography using a Poros R2 column 4.6 x 100 mm (Perseptive Biosystems). Polypeptides were eluted from the column with a linear gradient from 0-100% acetonitrile (0.1% TFA) at a flow rate of 5 ml/min. The eluent was monitored at 214 nm.

Fractions containing the eluted polypeptides were lyophilized and  
10 resuspended in 80 µl of aqueous 0.1% TFA and further subjected to reverse phase chromatography on a Vydac C4 column 4.6 x 150 mm (Western Analytical, Temecula, CA) with a linear gradient of 0-100% acetonitrile (0.1% TFA) at a flow rate of 2 ml/min. Eluent was monitored at 214 nm.

The fraction with biological activity was separated into one major peak  
15 plus other smaller components. Western blot of this peak onto PVDF membrane revealed three major bands of molecular weights 14 Kd, 20 Kd and 26 Kd. These polypeptides were determined to have the following N-terminal sequences, respectively:

- (j) Xaa-Asp-Ser-Glu-Lys-Ser-Ala-Thr-Ile-Lys-Val-Thr-Asp-Ala-Ser; (SEQ ID No. 134)
- 20 (k) Ala-Gly-Asp-Thr-Xaa-Ile-Tyr-Ile-Val-Gly-Asn-Leu-Thr-Ala-Asp; (SEQ ID No. 135) and
- (l) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 136), wherein Xaa may be any amino acid.

Using the assays described above, these polypeptides were shown to induce  
25 proliferation and IFN-γ production in PBMC preparations. Figs. 1A and B show the results of such assays using PBMC preparations from a first and a second donor, respectively.

DNA sequences that encode the antigens designated as (a), (c), (d) and  
(g) above were obtained by screening a genomic *M. tuberculosis* library using <sup>32</sup>P end  
30 labeled degenerate oligonucleotides corresponding to the N-terminal sequence and

containing *M. tuberculosis* codon bias. The screen performed using a probe corresponding to antigen (a) above identified a clone having the sequence provided in SEQ ID No. 101. The polypeptide encoded by SEQ ID No. 101 is provided in SEQ ID No. 102. The screen performed using a probe corresponding to antigen (g) above  
5 identified a clone having the sequence provided in SEQ ID No. 52. The polypeptide encoded by SEQ ID No. 52 is provided in SEQ ID No. 53. The screen performed using a probe corresponding to antigen (d) above identified a clone having the sequence provided in SEQ ID No. 24, and the screen performed with a probe corresponding to antigen (c) identified a clone having the sequence provided in SEQ ID No: 25.

10 The above amino acid sequences were compared to known amino acid sequences in the gene bank using the DNA STAR system. The database searched contains some 173,000 proteins and is a combination of the Swiss, PIR databases along with translated protein sequences (Version 87). No significant homologies to the amino acid sequences for antigens (a)-(h) and (l) were detected.

15 The amino acid sequence for antigen (i) was found to be homologous to a sequence from *M. leprae*. The full length *M. leprae* sequence was amplified from genomic DNA using the sequence obtained from GENBANK. This sequence was then used to screen the *M. tuberculosis* library described below in Example 2 and a full length copy of the *M. tuberculosis* homologue was obtained (SEQ ID No. 99).

20 The amino acid sequence for antigen (j) was found to be homologous to a known *M. tuberculosis* protein translated from a DNA sequence. To the best of the inventors' knowledge, this protein has not been previously shown to possess T-cell stimulatory activity. The amino acid sequence for antigen (k) was found to be related to a sequence from *M. leprae*.

25 In the proliferation and IFN- $\gamma$  assays described above, using three PPD positive donors, the results for representative antigens provided above are presented in Table 1:

TABLE 1  
RESULTS OF PBMC PROLIFERATION AND IFN- $\gamma$  ASSAYS

Sequence	Proliferation	IFN- $\gamma$
(a)	+	-
(c)	+++	+++
(d)	++	++
(g)	+++	+++
(h)	+++	+++

- 5 In Table 1, responses that gave a stimulation index (SI) of between 2 and 4 (compared to cells cultured in medium alone) were scored as +, an SI of 4-8 or 2-4 at a concentration of 1  $\mu$ g or less was scored as ++ and an SI of greater than 8 was scored as +++. The antigen of sequence (i) was found to have a high SI (+++) for one donor and lower SI (++ and +) for the two other donors in both proliferation and IFN- $\gamma$  assays.
- 10 These results indicate that these antigens are capable of inducing proliferation and/or interferon- $\gamma$  production.

### EXAMPLE 2

#### USE OF PATIENT SERA TO ISOLATE *M. TUBERCULOSIS* ANTIGENS

15

This example illustrates the isolation of antigens from *M. tuberculosis* lysate by screening with serum from *M. tuberculosis*-infected individuals.

- Dessicated *M. tuberculosis* H37Ra (Difco Laboratories) was added to a 2% NP40 solution, and alternately homogenized and sonicated three times. The
- 20 resulting suspension was centrifuged at 13,000 rpm in microfuge tubes and the supernatant put through a 0.2 micron syringe filter. The filtrate was bound to Macro Prep DEAE beads (BioRad, Hercules, CA). The beads were extensively washed with 20 mM Tris pH 7.5 and bound proteins eluted with 1M NaCl. The 1M NaCl elute was dialyzed overnight against 10 mM Tris, pH 7.5. Dialyzed solution was treated with

DNase and RNase at 0.05 mg/ml for 30 min. at room temperature and then with  $\alpha$ -D-mannosidase, 0.5 U/mg at pH 4.5 for 3-4 hours at room temperature. After returning to pH 7.5, the material was fractionated via FPLC over a Bio Scale-Q-20 column (BioRad). Fractions were combined into nine pools, concentrated in a Centriprep 10 (Amicon, Beverley, MA) and then screened by Western blot for serological activity using a serum pool from *M. tuberculosis*-infected patients which was not immunoreactive with other antigens of the present invention.

The most reactive fraction was run in SDS-PAGE and transferred to PVDF. A band at approximately 85 Kd was cut out yielding the sequence:

10 (m) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val: (SEQ ID No. 137), wherein Xaa may be any amino acid.

Comparison of this sequence with those in the gene bank as described above, revealed no significant homologies to known sequences.

15

### EXAMPLE 3

#### PREPARATION OF DNA SEQUENCES ENCODING *M. TUBERCULOSIS* ANTIGENS

This example illustrates the preparation of DNA sequences encoding *M. tuberculosis* antigens by screening a *M. tuberculosis* expression library with sera obtained from patients infected with *M. tuberculosis*, or with anti-sera raised against soluble *M. tuberculosis* antigens.

#### 25 A. PREPARATION OF *M. TUBERCULOSIS* SOLUBLE ANTIGENS USING RABBIT ANTI-SERA

Genomic DNA was isolated from the *M. tuberculosis* strain H37Ra. The DNA was randomly sheared and used to construct an expression library using the Lambda ZAP expression system (Stratagene, La Jolla, CA). Rabbit anti-sera was generated against secretory proteins of the *M. tuberculosis* strains H37Ra, H37Rv and Erdman by immunizing a rabbit with concentrated supernatant of the *M. tuberculosis* cultures. Specifically, the rabbit was first immunized subcutaneously with 200  $\mu$ g of

protein antigen in a total volume of 2 ml containing 10 µg muramyl dipeptide (Calbiochem, La Jolla, CA) and 1 ml of incomplete Freund's adjuvant. Four weeks later the rabbit was boosted subcutaneously with 100 µg antigen in incomplete Freund's adjuvant. Finally, the rabbit was immunized intravenously four weeks later with 50 µg protein antigen. The anti-sera were used to screen the expression library as described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. Bacteriophage plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and the nucleotide sequences of the *M. tuberculosis* clones deduced.

Thirty two clones were purified. Of these, 25 represent sequences that have not been previously identified in human *M. tuberculosis*. Recombinant antigens were expressed and purified antigens used in the immunological analysis described in Example 1. Proteins were induced by IPTG and purified by gel elution, as described in Skeiky et al., *J. Exp. Med.* 181:1527-1537, 1995. Representative sequences of DNA molecules identified in this screen are provided in SEQ ID Nos.: 1-25. The corresponding predicted amino acid sequences are shown in SEQ ID Nos. 63-87.

On comparison of these sequences with known sequences in the gene bank using the databases described above, it was found that the clones referred to hereinafter as TbRA2A, TbRA16, TbRA18, and TbRA29 (SEQ ID Nos. 76, 68, 70, 75) show some homology to sequences previously identified in *Mycobacterium leprae* but not in *M. tuberculosis*. TbRA11, TbRA26, TbRA28 and TbDPEP (SEQ ID Nos.: 65, 73, 74, 53) have been previously identified in *M. tuberculosis*. No significant homologies were found to TbRA1, TbRA3, TbRA4, TbRA9, TbRA10, TbRA13, TbRA17, TbRa19, TbRA29, TbRA32, TbRA36 and the overlapping clones TbRA35 and TbRA12 (SEQ ID Nos. 63, 77, 81, 82, 64, 67, 69, 71, 75, 78, 80, 79, 66). The clone TbRa24 is overlapping with clone TbRa29.

The results of PBMC proliferation and interferon-γ assays performed on representative recombinant antigens, and using T-cell preparations from several different *M. tuberculosis*-immune patients, are presented in Tables 2 and 3, respectively.

**TABLE 2**  
**RESULTS OF PBMC PROLIFERATION TO REPRESENTATIVE SOLUBLE ANTIGENS**

Antigen	Patient												
	1	2	3	4	5	6	7	8	9	10	11	12	13
TbRa1	-	-	±	++	-	-	±	±	-	-	+	±	-
TbRa3	-	±	++	-	±	-	-	++	±	-	-	-	-
TbRa9	-	-	nt	nt	++	++	nt	nt	nt	nt	nt	nt	nt
TbRa10	-	-	±	±	±	+	nt	±	-	+	±	±	-
TbRa11	±	±	+	++	++	+	nt	-	++	++	++	±	nt
TbRa12	-	-	+	+	±	++	+	±	±	-	+	-	-
TbRa16	nt	nt	nt	nt	-	+	nt	nt	nt	nt	nt	nt	nt
TbRa24	nt	nt	nt	nt	-	-	nt	nt	nt	nt	nt	nt	nt
TbRa26	-	+	nt	nt	-	-	nt	nt	nt	nt	nt	nt	nt
TbRa29	nt	nt	nt	nt	-	-	nt	nt	nt	nt	nt	nt	nt
TbRa35	++	nt	++	++	++	++	nt	++	++	++	++	++	nt
TbRaB	nt	nt	nt	nt	-	-	nt	nt	nt	nt	nt	nt	nt
TbRaC	nt	nt	nt	nt	-	-	nt	nt	nt	nt	nt	nt	nt
TbRaD	nt	nt	nt	nt	-	-	nt	nt	nt	nt	nt	nt	nt
AAMK	-	-	±	-	-	-	nt	-	-	-	nt	±	nt
YY	-	-	-	-	-	-	nt	-	-	-	nt	+	nt
DPEP	-	+	-	++	-	-	nt	++	±	+	±	±	nt
Control	-	-	-	-	-	-	-	-	-	-	-	-	-

nt = not tested



In Tables 2 and 3, responses that gave a stimulation index (SI) of between 1.2 and 2 (compared to cells cultured in medium alone) were scored as  $\pm$ , a SI of 2-4 was scored as +, as SI of 4-8 or 2-4 at a concentration of 1  $\mu$ g or less was scored as ++ and an SI of greater than 8 was scored as +++. In addition, the effect of concentration on proliferation and interferon- $\gamma$  production is shown for two of the above antigens in the attached Figure. For both proliferation and interferon- $\gamma$  production, TbRa3 was scored as ++ and TbRa9 as +.

These results indicate that these soluble antigens can induce proliferation and/or interferon- $\gamma$  production in T-cells derived from an *M. tuberculosis*-immune individual.

B. USE OF PATIENT SERA TO IDENTIFY DNA SEQUENCES ENCODING *M. TUBERCULOSIS* ANTIGENS

The genomic DNA library described above, and an additional H37Rv library, were screened using pools of sera obtained from patients with active tuberculosis. To prepare the H37Rv library, *M. tuberculosis* strain H37Rv genomic DNA was isolated, subjected to partial *Sau*3A digestion and used to construct an expression library using the Lambda Zap expression system (Stratagene, La Jolla, Ca). Three different pools of sera, each containing sera obtained from three individuals with active pulmonary or pleural disease, were used in the expression screening. The pools were designated TbL, TbM and TbH, referring to relative reactivity with H37Ra lysate (*i.e.*, TbL = low reactivity, TbM = medium reactivity and TbH = high reactivity) in both ELISA and immunoblot format. A fourth pool of sera from seven patients with active pulmonary tuberculosis was also employed. All of the sera lacked increased reactivity with the recombinant 38 kD *M. tuberculosis* H37Ra phosphate-binding protein.

All pools were pre-adsorbed with *E. coli* lysate and used to screen the H37Ra and H37Rv expression libraries, as described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. Bacteriophage plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and the nucleotide sequences of the *M. tuberculosis* clones deduced.

Thirty two clones were purified. Of these, 31 represented sequences that had not been previously identified in human *M. tuberculosis*. Representative sequences of the DNA molecules identified are provided in SEQ ID Nos.: 26-51 and 105. Of these, TbH-8 and TbH-8-2 (SEQ. ID NO. 105) are non-contiguous DNA sequences from the same clone, and TbH-4 (SEQ. ID NO. 43) and TbH-4-FWD (SEQ. ID NO. 44) are non-contiguous sequences from the same clone. Amino acid sequences for the antigens hereinafter identified as Tb38-1, TbH-4, TbH-8, TbH-9, and TbH-12 are shown in SEQ ID Nos.: 88-92. Comparison of these sequences with known sequences in the gene bank using the databases identified above revealed no significant homologies to TbH-4, TbH-8, TbH-9 and TbM-3, although weak homologies were found to TbH-9. TbH-12 was found to be homologous to a 34 kD antigenic protein previously identified in *M. paratuberculosis* (Acc. No. S28515). Tb38-1 was found to be located 34 base pairs upstream of the open reading frame for the antigen ESAT-6 previously identified in *M. bovis* (Acc. No. U34848) and in *M. tuberculosis* (Sorensen et al., *Infect. Immun.* 63:1710-1717, 1995).

Probes derived from Tb38-1 and TbH-9, both isolated from an H37Ra library, were used to identify clones in an H37Rv library. Tb38-1 hybridized to Tb38-1F2, Tb38-1F3, Tb38-1F5 and Tb38-1F6 (SEQ. ID NOS. 112, 113, 116, 118, and 119). (SEQ ID NOS. 112 and 113 are non-contiguous sequences from clone Tb38-1F2.) Two open reading frames were deduced in Tb38-1F2; one corresponds to Tb37FL (SEQ. ID. NO. 114), the second, a partial sequence, may be the homologue of Tb38-1 and is called Tb38-IN (SEQ. ID NO. 115). The deduced amino acid sequence of Tb38-1F3 is presented in SEQ. ID. NO. 117. A TbH-9 probe identified three clones in the H37Rv library: TbH-9-FL (SEQ. ID NO. 106), which may be the homologue of TbH-9 (R37Ra), TbH-9-1 (SEQ. ID NO. 108), and TbH-9-4 (SEQ. ID NO. 110), all of which are highly related sequences to TbH-9. The deduced amino acid sequences for these three clones are presented in SEQ ID NOS. 107, 109 and 111.

The results of T-cell assays performed on Tb38-1, ESAT-6 and other representative recombinant antigens are presented in Tables 4A, B and 5, respectively, below:

**TABLE 4A**  
RESULTS OF PBMC PROLIFERATION TO REPRESENTATIVE ANTIGENS

Antigen	Donor										
	1	2	3	4	5	6	7	8	9	10	11
Tb38.1	+++	+	-	-	-	++	-	+	-	++	+++
ESAT-6	+++	+	+	+	-	+	-	+	+	++	+++
TbH-9	++	++	-	++	±	±	++	++	++	++	++

5

**TABLE 4B**  
RESULTS OF PBMC INTERFERON- $\gamma$  PRODUCTION TO REPRESENTATIVE ANTIGENS

Antigen	Donor										
	1	2	3	4	5	6	7	8	9	10	11
Tb38.1	+++	+	-	+	+	+++	-	++	-	+++	+++
ESAT-6	+++	+	+	+	+-	+	-	+	+	+++	+++
TbH-9	++	++	-	+++	±	±	+++	+++	++	+++	++

10

**TABLE 5**  
**SUMMARY OF T-CELL RESPONSES TO REPRESENTATIVE ANTIGENS**

Antigen	Proliferation			Interferon- $\gamma$			total
	patient 4	patient 5	patient 6	patient 4	patient 5	patient 6	
TbH9	++	++	++	+++	++	++	13
TbM7	-	+	-	++	+	-	4
TbH5	-	+	+	++	++	++	8
TbL23	-	+	$\pm$	++	++	+	7.5
TbH4	-	++	$\pm$	++	++	$\pm$	7
- control	-	-	-	-	-	-	0

5

These results indicate that both the inventive *M. tuberculosis* antigens and ESAT-6 can induce proliferation and/or interferon- $\gamma$  production in T-cells derived from an *M. tuberculosis*-immune individual. To the best of the inventors' knowledge, ESAT-6 has not been previously shown to stimulate human immune responses

10

A set of six overlapping peptides covering the amino acid sequence of the antigen Tb38-1 was constructed using the method described in Example 4. The sequences of these peptides, hereinafter referred to as pep1-6, are provided in SEQ ID Nos. 93-98, respectively. The results of T-cell assays using these peptides are shown in Tables 6 and 7. These results confirm the existence, and help to localize T-cell epitopes within Tb38-1 capable of inducing proliferation and interferon- $\gamma$  production in T-cells derived from an *M. tuberculosis* immune individual.

15

**TABLE 6**  
**RESULTS OF PBMC PROLIFERATION TO TB38-1 PEPTIDES**

[illegible]



#### EXAMPLE 4

##### PURIFICATION AND CHARACTERIZATION OF A POLYPEPTIDE FROM TUBERCULIN PURIFIED PROTEIN DERIVATIVE

5

An *M. tuberculosis* polypeptide was isolated from tuberculin purified protein derivative (PPD) as follows.

PPD was prepared as published with some modification (Seibert, F. et al., Tuberculin purified protein derivative. Preparation and analyses of a large quantity  
10 for standard. The American Review of Tuberculosis 44:9-25, 1941).

*M. tuberculosis* Rv strain was grown for 6 weeks in synthetic medium in roller bottles at 37°C. Bottles containing the bacterial growth were then heated to 100°C in water vapor for 3 hours. Cultures were sterile filtered using a 0.22 µ filter and the liquid phase was concentrated 20 times using a 3 kD cut-off membrane. Proteins were  
15 precipitated once with 50% ammonium sulfate solution and eight times with 25% ammonium sulfate solution. The resulting proteins (PPD) were fractionated by reverse phase liquid chromatography (RP-HPLC) using a C18 column (7.8 x 300 mM; Waters, Milford, MA) in a Biocad HPLC system (Perseptive Biosystems, Framingham, MA). Fractions were eluted from the column with a linear gradient from 0-100% buffer (0.1%  
20 TFA in acetonitrile). The flow rate was 10 ml/minute and eluent was monitored at 214 nm and 280 nm.

Six fractions were collected, dried, suspended in PBS and tested individually in *M. tuberculosis*-infected guinea pigs for induction of delayed type hypersensitivity (DTH) reaction. One fraction was found to induce a strong DTH  
25 reaction and was subsequently fractionated further by RP-HPLC on a microbore Vydac C18 column (Cat. No. 218TP5115) in a Perkin Elmer/Applied Biosystems Division Model 172 HPLC. Fractions were eluted with a linear gradient from 5-100% buffer (0.05% TFA in acetonitrile) with a flow rate of 80 µl/minute. Eluent was monitored at 215 nm. Eight fractions were collected and tested for induction of DTH in *M.*  
30 *tuberculosis*-infected guinea pigs. One fraction was found to induce strong DTH of

about 16 mm induration. The other fractions did not induce detectable DTH. The positive fraction was submitted to SDS-PAGE gel electrophoresis and found to contain a single protein band of approximately 12 kD molecular weight.

This polypeptide, herein after referred to as DPPD, was sequenced from the amino terminal using a Perkin Elmer/Applied Biosystems Division Procise 492 protein sequencer as described above and found to have the N-terminal sequence shown in SEQ ID No.: 129. Comparison of this sequence with known sequences in the gene bank as described above revealed no known homologies. Four cyanogen bromide fragments of DPPD were isolated and found to have the sequences shown in SEQ ID Nos.: 130-133.

The ability of the antigen DPPD to stimulate human PBMC to proliferate and to produce IFN- $\gamma$  was assayed as described in Example 1. As shown in Table 8, DPPD was found to stimulate proliferation and elicit production of large quantities of IFN- $\gamma$ ; more than that elicited by commercial PPD.

TABLE 8

RESULTS OF PROLIFERATION AND INTERFERON- $\gamma$  ASSAYS TO DPPD

PBMC Donor	Stimulator	Proliferation (CPM)	IFN- $\gamma$ (OD <sub>450</sub> )
A	Medium	1,089	0.17
	PPD (commercial)	8,394	1.29
	DPPD	13,451	2.21
B	Medium	450	0.09
	PPD (commercial)	3,929	1.26
	DPPD	6,184	1.49
C	Medium	541	0.11
	PPD (commercial)	8,907	0.76
	DPPD	23,024	>2.70

EXAMPLE 5SYNTHESIS OF SYNTHETIC POLYPEPTIDES

5

Polypeptides may be synthesized on a Millipore 9050 peptide synthesizer using Fmoc chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray mass spectrometry and by amino acid analysis.

20

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purpose of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

- (i) APPLICANTS: Corixa Corporation
- (ii) TITLE OF INVENTION: COMPOUNDS AND METHODS FOR IMMUNOTHERAPY  
AND DIAGNOSIS OF TUBERCULOSIS
- (iii) NUMBER OF SEQUENCES: 137
- (iv) CORRESPONDENCE ADDRESS:
  - (A) ADDRESSEE: SEED and BERRY LLP
  - (B) STREET: 6300 Columbia Center, 701 Fifth Avenue
  - (C) CITY: Seattle
  - (D) STATE: Washington
  - (E) COUNTRY: USA
  - (F) ZIP: 98104-7092
- (v) COMPUTER READABLE FORM:
  - (A) MEDIUM TYPE: Floppy disk
  - (B) COMPUTER: IBM PC compatible
  - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
  - (D) SOFTWARE: PatentIn Release #1.0. Version #1.30
- (vi) CURRENT APPLICATION DATA:
  - (A) APPLICATION NUMBER:
  - (B) FILING DATE: 27-AUG-1996
  - (C) CLASSIFICATION:
- (viii) ATTORNEY/AGENT INFORMATION:
  - (A) NAME: Maki, David J.
  - (B) REGISTRATION NUMBER: 31,392
  - (C) REFERENCE/DOCKET NUMBER: 210121.411PC
- (ix) TELECOMMUNICATION INFORMATION:
  - (A) TELEPHONE: (206) 622-4900
  - (B) TELEFAX: (206) 682-6031

## (2) INFORMATION FOR SEQ ID NO:1:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 766 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CGAGGCACCG GTAGTTTGAA CCAAACGCAC AATCGACGGG CAAACGAACG GAAGAACACA	60
ACCATGAAGA TGGTGAAATC GATCGCCGCA GGTCTGACCG CCGCGGCTGC AATCGGCGCC	120
GCTGCGGCCG GTGTGACTTC GATCATGGCT GCGGGCCCGG TCGTATACCA GATGCAGCCG	180
GTCTCTTCG GCGCGCCACT GCCGTTGGAC CCGGCATCCG CCCCTGACGT CCCGACCGCC	240
GCCCAGTTGA CCAGCCTGCT CAACAGCCTC GCCGATCCCA ACGTGTCGTT TGCGAACAAAG	300
GGCAGTCTGG TCGAGGGCGG CATCGGGGGC ACCGAGGCGC GCATCGCCGA CCACAAGCTG	360
AAGAAGGCCG CCGAGCACGG GGATCTGCCG CTGTCTGTTCA GCGTGACGAA CATCCAGCCG	420
GCGGCCGCCG GTTCGGCCAC CGCCGACGTT TCCGTCTCGG GTCCGAAGCT CTCGTCGCCG	480
GTCACGCAGA ACGTCACGTT CGTGAATCAA GCGGGCTGGA TGCTGTCACG CGCATCGGCG	540
ATGGAGTTGC TGCAGGCCGC AGGGNAACTG ATTGGCGGGC CGGNTTCAGC CCGCTGTTCA	600
GCTACGCCGC CCGCCTGGTG ACGCGTCCAT GTCGAACACT CGCGCGTGTA GCACGGTGCG	660
GTNTGCGCAG GGNCGCACGC ACCGCCCGGT GCAAGCCGTC CTCGAGATAG GTGGTGNCTC	720
GNCACCAGNG ANCACCCCN NNTCGNCNNT TCTCGNTGNT GNATGA	766

## (2) INFORMATION FOR SEQ ID NO:2:

- (A) LENGTH: 752 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

ATGCATCACC ATCACCATCA CGATGAAGTC ACGGTAGAGA CGACCTCCGT CTTCCGCGCA	60
GACTTCCTCA GCGAGCTGGA CGCTCCTGCG CAAGCGGGTA CGGAGAGCGC GGTCTCCGGG	120
GTGGAAGGGC TCCCGCCGGG CTCGGCGTTG CTGGTAGTCA AACGAGGCC CAACGCCGGG	180
TCCCGGTTCC TACTCGACCA AGCCATCACG TCGGCTGGTC GGCATCCCGA CAGCGACATA	240
TTTCTCGACG ACGTGACCGT GAGCCGTCGC CATGCTGAAT TCCGGTTGGA AAACAACGAA	300
TTCAATGTCG TCGATGTCGG GAGTCTCAAC GGCACCTACG TCAACCGCGA GCCCGTGGAT	360
TCGGCGGTGC TGGCGAACGG CGACGAGGTC CAGATCGGCA AGCTCCGGTT GGTGTTCTTG	420
ACCGGACCCA AGCAAGGCGA GGATGACGGG AGTACCGGGG GCCCGTGAGC GCACCCGATA	480
GCCCCGCGCT GGCCGGGATG TCGATCGGGG CGGTCTCCG ACCTGCTACG ACCGGATTTT	540
CCCTGATGTC CACCATCTCC AAGATTCGAT TCTTGGGAGG CTTGAGGGTC NGGGTGACCC	600
CCCCGCGGGC CTCATTCNGG GGTNTCGGCN GGTTCACCC CNTACCNACT GCCNCCCGGN	660
TTGCNAATTC NTTCTTCNCT GCCCNAAAG GGACCNTTAN CTTGCCGCTN GAAANGGTNA	720
TCCNGGGCCC NTCCTNGAAN CCCCNTCCCC CT	752

## (2) INFORMATION FOR SEQ ID NO:3:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 813 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CATATGCATC ACCATCACCA TCACACTTCT AACCGCCCAG CGCGTCGGGG GCGTCGAGCA	60
CCACGCGACA CCGGGCCCGA TCGATCTGCT AGCTTGAGTC TGGTCAGGCA TCGTCGTCAG	120
CAGCGCGATG CCCTATGTTT GTCGTCGACT CAGATATCGC GGCAATCCAA TCTCCCGCCT	180
GCGGCCGGCG GTGCTGCAAA CTA CTCTCCCGG AGGAATTTCTG ACGTGCGCAT CAAGATCTTC	240
ATGCTGGTCA CGGCTGTCGT TTTGCTCTGT TGTTGCGGTG TGGCCACGGC CGCGCCCAAG	300
ACCTACTGCG AGGAGTTGAA AGGCACCGAT ACCGGCCAGG CGTGCCAGAT TCAAATGTCC	360
GACCCGGCCT ACAACATCAA CATCAGCCTG CCCAGTTACT ACCCCGACCA GAAGTCGCTG	420
GAAAATTACA TCGCCAGAC GCGCGACAAG TTCCTCAGCG CGGCCACATC GTCCACTCCA	480
CGCGAAGCCC CCTACGAATT GAATATCACC TCGGCCACAT ACCAGTCCGC GATACCGCCG	540
CGTGGTACGC AGGCCGTGGT GCTCAMGGTC TACCACAACG CCGGCGGCAC GCACCCAACG	600
ACCACGTACA AGGCCTTCGA TTGGGACCAG GCCTATCGCA AGCCAATCAC CTATGACACG	660
CTGTGGCAGG CTGACACCGA TCCGCTGCCA GTCGTCTTCC CCATTGTTGC AAGGTGAACT	720
GAGCAACGCA GACCGGGACA ACWGGTATCG ATAGCCGCCN AATGCCGGCT TGAACCCNG	780
TGAAATTATC ACAACTTCGC AGTCACNAAA NAA	813

## (2) INFORMATION FOR SEQ ID NO:4:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 447 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

CGGTATGAAC ACGGCCGCGT CCGATAACTT CCAGCTGTCC CAGGGTGGGC AGGGATTTCGC	60
CATTCCGATC GGGCAGGCGA TGGCGATCGC GGGCCAGATC CGATCGGGTG GGGGGTCACC	120
CACCGTTCAT ATCGGGCCTA CCGCCTTCCT CGGCTTGGGT GTTGTGACA ACAACGGCAA	180
CGGCGCACGA GTCCAACGCG TGGTCGGGAG CGCTCCGGCG GCAAGTCTCG GCATCTCCAC	240
CGGCGACGTG ATCACCGCGG TCGACGGCGC TCCGATCAAC TCGGCCACCG CGATGGCGGA	300
CGCGCTTAAC GGGCATCATC CCGGTGACGT CATCTCGGTG AACTGGCAA CCAAGTCGGG	360
CGGCACGCGT ACAGGGAACG TGACATTGGC CGAGGGACCC CCGGCCTGAT TTCGTCGYGG	420
ATACCACCCG CCGGCCGGCC AATTGGA	447

## (2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 604 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GTCCCACTGC GGTGCGCGAG TATGTCGCCC AGCAAATGTC TGGCAGCCGC CCAACGGAAT	60
CCGGTGATCC GACGTGCGAG GTTGTGCAAC CCGCCGCCGC GGAAGTATCG GTCCATGCCT	120
AGCCCGGGCGA CGGCGAGCGC CGGAATGGCG CGAGTGAGGA GGGGGCAAT TTGGCGGGGC	180
CCGGCGACGG NGAGCGCCGG AATGGCGCGA GTGAGGAGGT GGNAGTCAT GCCCAGNGTG	240
ATCCAATCAA CCTGNATTCG GNCTGNNGGN CCATTTGACA ATCGAGGTAG TGAGCGCAAA	300
TGAATGATGG AAAACGGGNG GNGACGTCCG NTGTTCTGGT GGTGNTAGGT GNCTGNCTGG	360

NGTNGNGGNT ATCAGGATGT TCTTCGNCGA AANCTGATGN CGAGGAACAG GGTGTNCCCG	420
NNANNCCNAN GGNGTCCNAN CCCNNNTCC TCGNCGANAT CANANAGNCG NTTGATGNGA	480
NAAAAGGGTG GANCAGNNNN AANTNGNGGN CCNAANAANC NNNANNGNNG NNAGNTNGNT	540
NNNTNTTNNC ANNNNNNTG NNGNNGNCCN NNNCAANCNN NTNNNNGNAA NNGGNTTNTT	600
NAAT	604

## (2) INFORMATION FOR SEQ ID NO:6:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 633 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

TTGCANGTCG AACACCTCA CTAAAGGGAA CAAAAGCTNG AGCTCCACCG CGGTGGCGGC	60
CGCTCTAGAA CTAGTGKATM YYYCKGGCTG CAGSAATYCG GYACGAGCAT TAGGACAGTC	120
TAACGGTCCT GTTACGGTGA TCGAATGACC GACGACATCC TGCTGATCGA CACCGACGAA	180
CGGGTGCGAA CCCTCACCT CAACGGGCGG CAGTCCCGYA ACGCGCTCTC GGCGGCGCTA	240
CGGGATCGGT TTTTCGCGGY GTTGGYCGAC GCCGAGGYCG ACGACGACAT CGACGTCGTC	300
ATCCTCACCG GYGCCGATCC GGTGTTCTGC GCCGACTGG ACCTCAAGGT AGCTGGCCGG	360
GCAGACCGCG CTGCCGACA TCTACCGCG GTGGGCGGCC ATGACCAAGC CGGTGATCGG	420
CGCGATCAAC GGCGCCGCGG TCACGGCGG GCTCGAACTG GCGCTGTACT GCGACATCCT	480
GATCGCCTCC GAGCACGCC GCTTCGNCGA CACCCACGCC CGGGTGGGGC TGCTGCCAC	540
CTGGGACTC AGTGTGTGCT TGCCGAAAA GGTGCGCATC GGNCTGGGCC GGTGGATGAG	600
CCTGACCGGC GACTACCTGT CCGTGACCGA CGC	633

## (2) INFORMATION FOR SEQ ID NO:7:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1362 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CGACGACGAC GGC GCCGAG AGCGGGCGCG AACGGCGATC GACGCGGCCC TGGCCAGAGT	60
CGGCACCACC CAGGAGGGAG TCGAATCATG AAATTTGTCA ACCATATTGA GCCCGTCGCG	120
CCCCGCCGAG CCGGCGGCGC GGTGCGCGAG GTCTATGCCG AGGCCCCCGG CGAGTTCGGC	180
CGGCTGCCCC AGCCGCTCGC CATGCTGTCC CCGGACGAGG GACTGCTCAC CGCCGGCTGG	240
GCGACGTTGC GCGAGACACT GCTGGTGGGC CAGGTGCCGC GTGGCCGCAA GGAAGCCGTC	300
GCCGCCGCCG TCGCGGCCAG CCTGCGCTGC CCCTGGTGCG TCGACGCACA CACCACCATG	360
CTGTACGCGG CAGGCCAAAC CGACACCGCC GCGGCGATCT TGGCCGGCAC AGCACCTGCC	420
GCCGGTGACC CGAACGCGCC GTATGTGGCG TGGGCGGCAG GAACCGGGAC ACCGGCGGGA	480
CCGCCGGCAC CGTTCGCCCC GGATGTCGCC GCCGAATACC TGGGCACCGC GGTGCAATTC	540
CACTTCATCG CACGCCTGGT CCTGGTGCTG CTGGACGAAA CCTTCCTGCC GGGGGGCCCCG	600
CGCGCCCAAC AGCTCATGCG CCGCGCCGGT GGA CTGGTGT TCGCCCGCAA GGTGCGCGCG	660
GAGCATCGGC CGGGCCGCTC CACCCGCCGG CTCGAGCCGC GAACGCTGCC CGACGATCTG	720
GCATGGGCAA CACCGTCCGA GCCCATAGCA ACCGCGTTCG CCGCGCTCAG CCACCACCTG	780
GACACCGCGC CGCACCTGCC GCCACCGACT CGTCAGGTGG TCAGGCGGGT CGTGGGGTGC	840
TGGCACGGCG AGCCAATGCC GATGAGCAGT CGCTGGACGA ACGAGCACAC CGCCGAGCTG	900

CCCGCCGACC TGCACGCGCC CACCCGTCTT GCCCTGCTGA CCGGCCTGGC CCCGCATCAG	960
GTGACCGACG ACGACGTCGC CGCGGCCCCGA TCCCTGCTCG ACACCGATGC GGCGCTGGTT	1020
GGCGCCCTGG CTTGGGCGCG CTTACCGGCC GCGCGGCGCA TCGGCACCTG GATCGGCGCC	1080
GCCGCCGAGG GCCAGGTGTC GCGGCAAAAC CCGACTGGGT GAGTGTGCGC GCCCTGTCGG	1140
TAGGGTGTCA TCGCTGGCCC GAGGGATCTC GCGGCGGCGA ACGGAGGTGG CGACACAGGT	1200
GGAAGCTGCG CCCACTGGCT TCGCCCCAA CGCCGTCGTG GCGGTTGGT TGGCCGCACT	1260
GGCCGATCAG GTCGGCGCCG GCCCTTGCC GAAGGTCCAG CTCAACGTGC CGTCACCGAA	1320
GGACCGGACG GTCACCGGGG GTCACCCTGC GCGCCAAGG AA	1362

## (2) INFORMATION FOR SEQ ID NO:8:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1458 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GCGACGACCC CGATATGCCG GGCACCGTAG CGAAAGCCGT CGCCGACGCA CTCGGGCGCG	60
GTATCGCTCC CGTTGAGGAC ATTCAGGACT GCGTGGAGGC CCGGCTGGGG GAAGCCGGTC	120
TGGATGACGT GGCCCGTGTT TACATCATCT ACCGGCAGCG GCGCGCCGAG CTGCGGACGG	180
CTAAGGCCTT GCTCGGCGTG CGGGACGAGT TAAAGCTGAG CTTGGCGGCC GTGACGGTAC	240
TGCGCGAGCG CTATCTGCTG CACGACGAGC AGGGCCGGCC GGCCGAGTCG ACCGGCGAGC	300
TGATGGACCG ATCGGCGCGC TGTGTCGCGG CGGCCGAGGA CCAGTATGAG CCGGGCTCGT	360
CGAGGCGGTG GGCCGAGCGG TTCGCCACGC TATTACGCAA CCTGGAATTC CTGCCGAATT	420
CGCCCACGTT GATGAACTCT GGCACCGACC TGGGACTGCT CGCCGGCTGT TTTGTTCTGC	480

CGATTGAGGA TTCGCTGCAA TCGATCTTTG CGACGCTGGG ACAGGCCGCC GAGCTGCAGC	540
GGGCTGGAGG CGGCACCGGA TATGCGTTCA GCCACCTGCG ACCCGCCGGG GATCGGGTGG	600
CCTCCACGGG CGGCACGGCC AGCGGACCGG TGTCGTTTCT ACGGCTGTAT GACAGTGCCG	660
CGGGTGTGGT CTCCATGGGC GGTCGCCGGC GTGGCGCCTG TATGGCTGTG CTTGATGTGT	720
CGCACCCGGA TATCTGTGAT TTCGTCACCG CCAAGGCCGA ATCCCCAGC GAGCTCCCGC	780
ATTTCAACCT ATCGGTTGGT GTGACCGACG CGTTCCTGCG GGCCGTCGAA CGCAACGGCC	840
TACACCGGCT GGTCAATCCG CGAACCGGCA AGATCGTCGC GCGGATGCCC GCCGCCGAGC	900
TGTTCGACGC CATCTGCAAA GCCGCGCAGC CCGGTGGCGA TCCCGGGCTG GTGTTTCTCG	960
ACACGATCAA TAGGGCAAAC CCGGTGCCGG GGAGAGGCCG CATCGAGGCG ACCAACCCGT	1020
GCGGGGAGGT CCCACTGCTG CCTTACGAGT CATGTAATCT CGGCTCGATC AACCTCGCCC	1080
GGATGCTCGC CGACGGTCGC GTCGACTGGG ACCGGCTCGA GGAGGTCGCC GGTGTGGCGG	1140
TGCGGTTTCCT TGATGACGTC ATCGATGTCA GCCGCTACCC CTTCCCCGAA CTGGGTGAGG	1200
CGGCCCCGCGC CACCCGCAAG ATCGGGCTGG GAGTCATGGG TTTGGCGGAA CTGCTTGCCG	1260
CACTGGGTAT TCCGTACGAC AGTGAAGAAG CCGTGCGGTT AGCCACCCGG CTCATGCGTC	1320
GCATACAGCA GGCGGCGCAC ACGGCATCGC GGAGGCTGGC CGAAGAGCGG GGCGCATTCC	1380
CGGCGTTCAC CGATAGCCGG TTCGCGCGGT CGGGCCCGAG GCGCAACGCA CAGGTCACCT	1440
CCGTCGCTCC GACGGGCA	1458

## (2) INFORMATION FOR SEQ ID NO:9:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 862 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

ACGGTGTAAT C	GTGCTGGAT CTGGAACCGC GTGGCCCGCT ACCTACCGAG ATCTACTGGC	60
GGCGCAGGGG G	CTGGCCCTG GGCATCGCGG TCGTCGTAGT CGGGATCGCG GTGGCCATCG	120
TCATCGCCTT C	GTGACAGC AGCGCCGGTG CCAAACCGGT CAGCGCCGAC AAGCCGGCCT	180
CCGCCCAGAG C	CATCCGGGC TCGCCGGCAC CCAAGCACC CCAGCCGGCC GGGCAAACCG	240
AAGGTAACGC C	GCGCGGGCC CCGCCGAGG GCCAAAACCC CGAGACACCC ACGCCACCG	300
CCGCGGTGCA G	CCCGCCCGG GTGCTCAAGG AAGGGGACGA TTGCCCCGAT TCGACGCTGG	360
CCGTCAAAGG T	TTGACCAAC GCGCCGAGT ACTACGTCGG CGACCAGCCG AAGTTCACCA	420
TGGTGGTCAC C	AACATCGGC CTGGTGTCTT GTAAACGCGA CGTTGGGGCC GCGGTGTTGG	480
CCGCCTACGT T	ACTCGCTG GACAACAAGC GGTGTGGTC CAACCTGGAC TCGCGCCCT	540
CGAATGAGAC G	CTGGTCAAG ACGTTTTCCC CCGGTGAGCA GGTAACGACC GCGGTGACCT	600
GGACCGGGAT G	GGATCGGCG CCGCGCTGCC CATTGCCGCG GCCGGCGATC GGGCCGGGCA	660
CCTACAATCT C	GTGGTACAA CTGGGCAATC TGCCTCGCT GCCGGTTCG TTCATCCTGA	720
ATCAGCCGCC G	CCGCCGCC GGGCCGGTAC CCGCTCCGGG TCCAGCGCAG GCGCCTCCGC	780
CGGAGTCTCC C	GCGCAAGGC GGATAATTAT TGATCGCTGA TGGTCGATTC CGCCAGCTGT	840
GACAACCCCT C	GCCTCGTGC CG	862

## (2) INFORMATION FOR SEQ ID NO:10:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 622 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

TTGATCAGCA CCGGCAAGGC GTCACATGCC TCCCTGGGTG TGCAGGTGAC CAATGACAAA	60
GACACCCCGG GCGCCAAGAT CGTCGAAGTA GTGGCCGGTG GTGCTGCCGC GAACGCTGGA	120
GTGCCGAAGG GCGTCGTTGT CACCAAGGTC GACGACCGCC CGATCAACAG CGCGGACGCG	180
TTGGTTGCCG CCGTGCGGTC CAAAGCGCCG GGC GCCACGG TGGCGCTAAC CTTTCAGGAT	240
CCCTCGGGCG GTAGCCGCAC AGTGCAAGTC ACCCTCGGCA AGGCGGAGCA GTGATGAAGG	300
TCGCCGCGCA GTGTTCAAAG CTCGGATATA CGGTGGCACC CATGGAACAG CGTGCGGAGT	360
TGGTGGTTGG CCGGGCACTT GTCGTCGTG TTAGCATCG CACGGCGCAC GGCGATGAAG	420
ACCACAGCGG GCCGCTTGTC ACCGAGCTGC TCACCGAGGC CGGGTTTGTT GTCGACGGCG	480
TGGTGGCGGT GTCGGCCGAC GAGGTCGAGA TCCGAAATGC GCTGAACACA GCGGTGATCG	540
GCGGGGTGGA CCTGGTGGTG TCGGTCGGCG GGACCGGNGT GACGNCTCGC GATGTCACCC	600
CGGAAGCCAC CCGNGACATT CT	622

## (2) INFORMATION FOR SEQ ID NO:11:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1200 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GGCGCAGCGG TAAGCCTGTT GGCCGCCGGC AACTGGTGT TGACAGCATG CGGCGGTGGC	60
ACCAACAGCT CGTCGTCAGG CGCAGGCGGA ACGTCTGGGT CGGTGCACTG CGGCGGCAAG	120
AAGGAGCTCC ACTCCAGCGG CTCGACCGCA CAAGAAAATG CCATGGAGCA GTTCGTCTAT	180

GCCTACGTGC GATCGTGCCC GGGCTACACG TTGGACTACA ACGCCAACGG GTCCGGTGCC	240
GGGGTGACCC AGTTTCTCAA CAACGAAACC GATTTGCGCG GCTCGGATGT CCCGTTGAAT	300
CCGTCGACCG GTCAACCTGA CCGGTCGGCG GAGCGGTGCG GTTCCCCGGC ATGGGACCTG	360
CCGACGGTGT TCGGCCCGAT CGCGATCACC TACAATATCA AGGGCGTGAG CACGCTGAAT	420
CTTGACGGAC CCACTACCGC CAAGATTTTC AACGGCACCA TCACCGTGTG GAATGATCCA	480
CAGATCCAAG CCCTCAACTC CGGCACCGAC CTGCCGCCAA CACCGATTAG CGTTATCTTC	540
CGCAGCGACA AGTCCGGTAC GTCGGACAAC TTCCAGAAAT ACCTCGACGG TGTATCCAAC	600
GGGGCGTGGG GCAAAGGCGC CAGCGAAACG TTCAGCGGGG GCGTCGGCGT CGGCGCCAGC	660
GGGAACAACG GAACGTCGGC CCTACTGCAG ACGACCGACG GGTGATCAC CTACAACGAG	720
TGGTCGTTTG CGGTGGGTAA GCAGTTGAAC ATGGCCCAGA TCATCACGTC GGCGGGTCCG	780
GATCCAGTGG CGATCACCAC CGAGTCGGTC GGTAAGACAA TCGCCGGGGC CAAGATCATG	840
GGACAAGGCA ACGACCTGGT ATTGGACACG TCGTCGTTCT ACAGACCCAC CCAGCCTGGC	900
TCTTACCCGA TCGTGCTGGC GACCTATGAG ATCGTCTGCT CGAAATACCC GGATGCGACG	960
ACCGGTACTG CGGTAAGGGC GTTTATGCAA GCCGCGATTG GTCCAGGCCA AGAAGGCCTG	1020
GACCAATACG GCTCCATTCC GTTGCCCAA TCGTTCCAAG CAAAATTGGC GGCCGCGGTG	1080
AATGCTATTT CTTGACCTAG TGAAGGGAAT TCGACGGTGA GCGATGCCGT TCCGCAGGTA	1140
GGGTCGCAAT TTGGGCCGTA TCAGCTATTG CGGCTGCTGG GCCGAGGCGG GATGGGCGAG	1200

## (2) INFORMATION FOR SEQ ID NO:12:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1155 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GCAAGCAGCT G̃CAGGTCGTG CTGTTGACG AACTGGGCAT GCCGAAGACC AAACGCACCA	60
AGACCGGCTA CACCACGGAT GCCGACGCGC TGCAGTCGTT GTTCGACAAG ACCGGGGCATC	120
CGTTTCTGCA ACATCTGCTC GCCCACC GCG ACGTCACCCG GCTCAAGGTC ACCGTCGACG	180
GGTTGCTCCA AGCGGTGGCC GCCGACGGCC GCATCCACAC CACGTTCAAC CAGACGATCG	240
CCGCGACCGG CCGGCTCTCC TCGACCGAAC CCAACCTGCA GAACATCCCG ATCCGCACCG	300
ACGCGGGCCG GCGGATCCGG GACGCGTTG TGGTCGGGGA CGGTTACGCC GAGTTGATGA	360
CGGCCGACTA CAGCCAGATC GAGATGCGGA TCATGGGGCA CCTGTCCGGG GACGAGGGCC	420
TCATCGAGGC GTTCAACACC GGGGAGGACC TGTATTGTT CGTCGCGTCC CGGGTGTTG	480
GTGTGCCCAT CGACGAGGTC ACCGGCGAGT TGCGGCGCCG GGTCAAGGCG ATGTCTACG	540
GGCTGGTTTA CGGGTTGAGC GCCTACGGCC TGTCGCAGCA GTTGAAAATC TCCACCGAGG	600
AAGCCAACGA GCAGATGGAC GCGTATTTG CCCGATTCGG CGGGGTGCGC GACTACCTGC	660
GCGCCGTAGT CGAGCGGGCC CGCAAGGACG GCTACACCTC GACGGTGCTG GGCCGTCGCC	720
GCTACCTGCC CGAGCTGGAC AGCAGCAACC GTCAAGTGCG GGAGGCCGCC GAGCGGGCGG	780
CGCTGAACGC GCCGATCCAG GGCAGCGCGG CCGACATCAT CAAGGTGGCC ATGATCCAGG	840
TCGACAAGGC GCTCAACGAG GCACAGCTGG CGTCGCGCAT GCTGCTGCAG GTCCACGACG	900
AGCTGCTGTT CGAAATCGCC CCCGGTGAAC GCGAGCGGGT CGAGGCCCTG GTGCGCGACA	960
AGATGGGCGG CGCTTACCCG CTCGACGTCC CGCTGGAGGT GTCGGTGGGC TACGGCCGCA	1020
GCTGGGACGC GGC GGCGCAC TGAGTGCCGA GCGTGCATCT GGGGCGGGAA TTCGGCGATT	1080
TTTCCGCCCT GAGTTCACGC TCGGCGCAAT CGGGACCGAG TTTGTCCAGC GTGTACCCGT	1140
CGAGTAGCCT CGTCA	1155

(2) INFORMATION FOR SEQ ID NO:13:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1771 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GAGCGCCGTC TGGTGTTTGA ACGGTTTTAC CGGTCGGCAT CGGCACGGGC GTTGCCGGGT	60
TCGGGCCTCG GGTGCGGAT CGTCAAACAG GTGGTGCTCA ACCACGGCGG ATTGCTGCGC	120
ATCGAAGACA CCGACCCAGG CGGCCAGCCC CCTGGAACGT CGATTTACGT GCTGCTCCCC	180
GGCCGTCGGA TGCCGATTCC GCAGCTTCCC GGTGCGACGG CTGGCGCTCG GAGCACGGAC	240
ATCGAGAACT CTCGGGGTTC GGCGAACGTT ATCTCAGTGG AATCTCAGTC CACGCGCGCA	300
ACCTAGTTGT GCAGTTACTG TTGAAAGCCA CACCCATGCC AGTCCACGCA TGGCCAAGTT	360
GGCCCGAGTA GTGGGCCTAG TACAGGAAGA GCAACCTAGC GACATGACGA ATCACCACAG	420
GTATTCGCCA CCGCCGCAGC AGCCGGGAAC CCCAGGTTAT GCTCAGGGGC AGCAGCAAAC	480
GTACAGCCAG CAGTTCGACT GGC GTTACCC ACCGTCCCCG CCCCCGCAGC CAACCCAGTA	540
CCGTCAACCC TACGAGGCGT TGGGTGGTAC CCGGCCGGGT CTGATACCTG GCGTGATTCC	600
GACCATGACG CCCCCTCCTG GGATGGTTCG CCAACGCCCT CGTGCAGGCA TGTTGGCCAT	660
CGGCGCGGTG ACGATAGCGG TGGTGTCCGC CGGCATCGGC GGC GCGGCCG CATCCCTGGT	720
CGGGTTCAAC CGGGCACCCG CCGGCCCCAG CGGCGGCCCA GTGGCTGCCA GCGCGGCGCC	780
AAGCATCCCC GCAGCAAACA TGCCGCCGGG GTCGGTCGAA CAGGTGGCGG CCAAGGTGGT	840
GCCCAGTGTC GTCATGTTGG AAACCGATCT GGGCCGCCAG TCGGAGGAGG GCTCCGGCAT	900
CATTCTGTCT GCCGAGGGGC TGATCTTGAC CAACAACCAC GTGATCGCGG CGGCCGCCAA	960

GCCTCCCCTG GGCAGTCCGC CGCCGAAAAC GACGGTAACC TTCTCTGACG GGCGGACCGC	1020
ACCCTTCACG GTGGTGGGG CTGACCCAC CAGTGATATC GCCGTCGTCC GTGTTCAGGG	1080
CGTCTCCGGG CTCACCCCGA TCTCCCTGGG TTCCTCCTCG GACCTGAGGG TCGGTCAGCC	1140
GGTGCTGGCG ATCGGGTCGC CGCTCGGTTT GGAGGGCACC GTGACCACGG GGATCGTCAG	1200
CGCTCTCAAC CGTCCAGTGT CGACGACCGG CGAGGCCGGC AACCAGAACA CCGTGCTGGA	1260
CGCCATTCAG ACCGACGCCG CGATCAACCC CGGTA ACTCC GGGGGCGCGC TGGTGAACAT	1320
GAACGCTCAA CTCGTGGAG TCAACTCGGC CATTGCCACG CTGGGCGCGG ACTCAGCCGA	1380
TGCGCAGAGC GGCTCGATCG GTCTCGGTTT TGCGATTCCA GTCGACCAGG CCAAGCGCAT	1440
CGCCGACGAG TTGATCAGCA CCGGCAAGGC GTCACATGCC TCCCTGGGTG TGCAGGTGAC	1500
CAATGACAAA GACACCCCGG GCGCCAAGAT CGTCGAAGTA GTGGCCGGTG GTGCTGCCGC	1560
GAACGCTGGA GTGCCGAAGG GCGTCGTTGT CACCAAGGTC GACGACGCC CGATCAACAG	1620
CGCGGACGCG TTGGTTGCCG CCGTGCGGTC CAAAGCGCCG GCGGCCACGG TGGCGCTAAC	1680
CTTTCAGGAT CCCTCGGGCG GTAGCCGCAC AGTGCAAGTC ACCCTCGGCA AGGCGGAGCA	1740
GTGATGAAGG TCGCCGCGCA GTGTTCAAAG C	1771

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1058 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

CTCCACCGCG GTGGCGGCCG CTCTAGAACT AGTGGATCCC CCGGGCTGCA GGAATTCGGC	60
ACGAGGATCC GACGTCGCAG GTTGTCGAAC CCGCCGCCGC GGAAGTATCG GTCCATGCCT	120

AGCCCGGCGA CGGCGAGCGC CGGAATGGCG CGAGTGAGGA GGCGGGCAAT TTGGCGGGGC	180
CCGGCGACGG CGAGCGCCGG AATGGCGCGA GTGAGGAGGC GGGCAGTCAT GCCCAGCGTG	240
ATCCAATCAA CCTGCATTCG GCCTGCGGGC CCATTTGACA ATCGAGGTAG TGAGCGCAAA	300
TGAATGATGG AAAACGGGCG GTGACGTCCG CTGTTCTGGT GGTGCTAGGT GCCTGCCTGG	360
CGTTGTGGCT ATCAGGATGT TCTTCGCCGA AACCTGATGC CGAGGAACAG GGTGTTCCCG	420
TGAGCCCGAC GGGTCCGAC CCCGCGCTCC TCGCCGAGAT CAGGCAGTCG CTTGATGCGA	480
CAAAAGGGTT GACCAGCGTG CACGTAGCGG TCCGAACAAC CGGGAAAGTC GACAGCTTGC	540
TGGGTATTAC CAGTGCCGAT GTCGACGTCC GGGCCAATCC GCTCGCGGCA AAGGGCGTAT	600
GCACCTACAA CGACGAGCAG GGTGTCCCGT TTCGGGTACA AGGCGACAAC ATCTCGGTGA	660
AACTGTTCGA CGACTGGAGC AATCTCGGCT CGATTTCTGA ACTGTCAACT TCACGCGTGC	720
TCGATCCTGC CGCTGGGGTG ACGCAGCTGC TGTCCGGTGT CACGAACCTC CAAGCGCAAG	780
GTACCGAAGT GATAGACGGA ATTTGACCA CAAAATCAC CGGGACCATC CCCGCGAGCT	840
CTGTCAAGAT GCTTGATCCT GGCGCCAAGA GTGCAAGGCC GGCGACCGTG TGGATTGCCC	900
AGGACGGGCTC GCACCACCTC GTCCGAGCGA GCATCGACCT CGGATCCGGG TCGATTCAGC	960
TCACGCAGTC GAAATGGAAC GAACCCGTCA ACGTCGACTA GGCCGAAGTT GCGTCGACGC	1020
GTTGNTCGAA ACGCCCTTGT GAACGGTGTC AACGGNAC	1058

(2) INFORMATION FOR SEQ ID NO:15:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 542 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GAATTCGGCA CGAGAGGTGA TCGACATCAT CGGGACCAGC CCCACATCCT GGGAAACAGGC	60
GGCGGCGGAG GCGGTCCAGC GGGCGCGGGA TAGCGTCGAT GACATCCGCG TCGCTCGGGT	120
CATTGAGCAG GACATGGCCG TGGACAGCGC CGGCAAGATC ACCTACCGCA TCAAGCTCGA	180
AGTGTCGTTT AAGATGAGGC CGGCGCAACC GCGCTAGCAC GGGCCGGCGA GCAAGACGCA	240
AAATCGCACG GTTTGCGGTT GATTCGTGCG ATTTTGTGTC TGCTCGCCGA GGCCTACCAG	300
GCGCGGCCCA GGTCCGCGTG CTGCCGTATC CAGGCGTGCA TCGCGATTCC GGCGCCACG	360
CCGGAGTTAA TGCTTCGCGT CGACCCGAAC TGGGCGATCC GCCGGNGAGC TGATCGATGA	420
CCGTGGCCAG CCCGTCGATG CCCGAGTTGC CCGAGGAAAC GTGCTGCCAG GCCGGTAGGA	480
AGCGTCCGTA GGCGGCGGTG CTGACCGGCT CTGCCTGCGC CCTCAGTGCG GCCAGCGAGC	540
GG	542

## (2) INFORMATION FOR SEQ ID NO:16:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 913 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CGGTGCCGCC CGCGCCTCCG TTGCCCCCAT TGCCGCCGTC GCCGATCAGC TGCGCATCGC	60
CACCATCACC GCCTTTGCCG CCGGCACCGC CGGTGGCGCC GGGGCCGCCG ATGCCACCGC	120
TTGACCCTGG CCGCCGGCGC CGCCATTGCC ATACAGCACC CCGCCGGGGG CACCGTTACC	180
GCCGTCGCCA CCGTCGCCGC CGCTGCCGTT TCAGGCCGGG GAGGCCGAAT GAACCGCCGC	240
CAAGCCCGCC GCCGGCACCG TTGCCGCCTT TTCCGCCCGC CCCGCCGGCG CCGCCAATTG	300

CCGAACAGCC AMGCACCGTT GCCGCCAGCC CCGCCGCCGT TAACGGCGCT GCCGGGCGCC	360
GCCGCCGGAC CCGCCATTAC CGCCGTTCCC GTTCGGTGCC CCGCCGTTAC CGGCGCCGCC	420
GTTTGCCGCC AATATTCGGC GGGCACC GCC AGACCCGCC GGGCCACCAT TGCCGCCGGG	480
CACCGAAACA ACAGCCCAAC GGTGCCGCCG GCGCCGCCGT TTGCCGCCAT CACCGGCCAT	540
TCACCGCCAG CACCGCCGTT AATGTTTATG AACCCGGTAC CGCCAGCGCG GCGCCTATTG	600
CGGGGCGCCG GAGNGCGTGC CCGCCGGCGC CGCCAACGCC CAAAAGCCCG GGGTTGCCAC	660
CGGCCCCGCC GGACCCACCG GTCCCGCCGA TCCCCCGTT GCCGCCGGTG CCGCCGCCAT	720
TGGTGCTGCT GAAGCCGTTA GCGCCGGTTC CGCSGGTTCC GGCGGTGGCG CCNTGGCCGC	780
CGGCCCCGCC GTTGCCGTAC AGCCACCCCC CGGTGGCGCC GTTGCCGCCA TTGCCGCCAT	840
TGCCGCCGTT GCCGCCATTG CCGCCGTTCC CGCCGCCACC GCCGGNTTGG CCGCCGGCGC	900
CGCCGGCGGC CGC	913

## (2) INFORMATION FOR SEQ ID NO:17:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1872 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GACTACGTTG GTGTAGAAAA ATCCTGCCGC CCGGACCCTT AAGGCTGGGA CAATTTCTGA	60
TAGCTACCCC GACACAGGAG GTTACGGGAT GAGCAATTCG CGCCGCCGCT CACTCAGGTG	120
GTCATGGTTG CTGAGCGTGC TGGCTGCCGT CGGGCTGGGC CTGGCCACGG CGCCGGCCCA	180
GGCGGCCCCG CCGGCCTTGT CGCAGGACCG GTTCGCCGAC TTCCCCGCGC TGCCCCCTGA	240

CCCGTCCGCG ATGGTCGCCC AAGTGGCGCC ACAGGTGGTC AACATCAACA CCAAACCTGGG	300
CTACAACAAC GCCGTGGGCG CCGGGACCGG CATCGTCATC GATCCCAACG GTGTCGTGCT	360
GACCAACAAC CACGTGATCG CGGGCGCCAC CGACATCAAT GCGTTCAGCG TCGGCTCCGG	420
CCAAACCTAC GGCCTCGATG TGGTCGGGTA TGACCGCACC CAGGATGTCG CGGTGCTGCA	480
GCTGCGCGGT GCCGGTGGCC TGCCGTGGC GGCATCGGT GGC GGCGTCG CGGTTGGTGA	540
GCCCGTCGTC GCGATGGGCA ACAGCGGTGG GCAGGGCGGA ACGCCCCGTG CGGTGCCTGG	600
CAGGGTGGTC GCGCTCGGCC AAACCGTGCA GGCCTCGGAT TCGCTGACCG GTGCCGAAGA	660
GACATTGAAC GGGTTGATCC AGTTCGATGC CGCAATCCAG CCCGGTGATT CGGGCGGGCC	720
CGTCGTCAAC GGCCTAGGAC AGGTGGTCGG TATGAACACG GCCGCGTCCG ATAACCTCCA	780
GCTGTCCCAG GGTGGGCAGG GATTGCGCAT TCCGATCGGG CAGGCGATGG CGATCGCGGG	840
CCAAATCCGA TCGGGTGGGG GGTACCCAC CGTTCATATC GGGCCTACCG CCTTCCTCGG	900
CTTGGGTGTT GTCGACAACA ACGGCAACGG CGCACGAGTC CAACGCGTGG TCGGAAGCGC	960
TCCGGCGGCA AGTCTCGGCA TCTCCACCGG CGACGTGATC ACCGCGGTCG ACGGCGCTCC	1020
GATCAACTCG GCCACCGCGA TGGCGGACGC GCTTAACGGG CATCATCCCG GTGACGTCAT	1080
CTCGGTGAAC TGGCAAACCA AGTCGGGCGG CACGCGTACA GGGAAAGTGA CATTGGCCGA	1140
GGGACCCCCG GCCTGATTTG TCGCGGATAC CACCCGCCGG CCGGCCAATT GGATTGGCGC	1200
CAGCCGTGAT TGCCGCGTGA GCCCCGAGT TCCGTCTCCC GTGCGCGTGG CATTGTGGAA	1260
GCAATGAACG AGGCAGAACA CAGCGTTGAG CACCCTCCCG TGCAGGGCAG TTACGTCGAA	1320
GGCGGTGTGG TCGAGCATCC GGATGCCAAG GACTTCGGCA GCGCCGCCGC CCTGCCCCGC	1380
GATCCGACCT GGTTTAAGCA CGCCGTCTTC TACGAGGTGC TGGTCCGGGC GTTCTTCGAC	1440
GCCAGCGCGG ACGGTTCCGN CGATCTGCGT GGAATCATCG ATCGCCTCGA CTACCTGCAG	1500
TGGCTTGGA TCGACTGCAT CTGTTGCCGC CGTTCCTACG ACTACCGCT GCGCGACGGC	1560
GGTTACGACA TTCGCGACTT CTACAAGGTG CTGCCGAAT TCGGCACCGT CGACGATTTT	1620

GTCGCCCTGG TCGACACCGC TCACCGGCGA GGTATCCGCA TCATCACCGA CCTGGTGATG	1680
AATCACACCT CGGAGTCGCA CCCCTGGTTT CAGGAGTCCC GCCGCGACCC AGACGGACCG	1740
TACGGTGACT ATTACGTGTG GAGCGACACC AGCGAGCGCT ACACCGACGC CCGGATCATC	1800
TTCGTCGACA CCGAAGAGTC GAACTGGTCA TTCGATCCTG TCCGCCGACA GTTNCTACTG	1860
GCACCGATTG TT	1872

## (2) INFORMATION FOR SEQ ID NO:18:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1482 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CTTCGCCGAA ACCTGATGCC GAGGAACAGG GTGTTCCCGT GAGCCCGACG GCGTCCGACC	60
CCGCGCTCCT CGCCGAGATC AGGCAGTCGC TTGATGCGAC AAAAGGGTTG ACCAGCGTGC	120
ACGTAGCGGT CCGAACAACC GGGAAAGTCG ACAGCTTGCT GGGTATTACC AGTGCCGATG	180
TCGACGTCCG GGCCAATCCG CTCGCGGCAA AGGGCGTATG CACCTACAAC GACGAGCAGG	240
GTGTCCCGTT TCGGGTACAA GGCGACAACA TCTCGGTGAA ACTGTTGAC GACTGGAGCA	300
ATCTCGGCTC GATTTCTGAA CTGTCAACTT CACGCGTGCT CGATCCTGCC GCTGGGGTGA	360
CGCAGCTGCT GTCCGGTGTC ACGAACCTCC AAGCGCAAGG TACCGAAGTG ATAGACGGAA	420
TTTCGACCAC CAAAATCACC GGGACCATCC CCGCGAGCTC TGTCAAGATG CTTGATCCTG	480
GCGCCAAGAG TGCAAGGCCG GCGACCGTGT GGATTGCCCA GGACGGCTCG CACCACCTCG	540
TCCGAGCGAG CATCGACCTC GGATCCGGGT CGATTGAGCT CACGCAGTCG AAATGGAACG	600

AACCCGTCAA CGTCGACTAG GCCGAAGTTG CGTCGACGCG TTGCTCGAAA CGCCCTTGTG	660
AACGGTGTCA ACGGCACCCG AAAACTGACC CCCTGACGGC ATCTGAAAAT TGACCCCTA	720
GACCGGGCGG TTGGTGGTTA TTCTTCGGTG GTTCCGGCTG GTGGGACGCG GCCGAGGTCG	780
CGGTCTTTGA GCCGGTAGCT GTCGCCTTTG AGGGCGACGA CTTCAGCATG GTGGACGAGG	840
CGGTCGATCA TGGCGGCAGC AACGACGTCG TCGCCGCCGA AAACCTCGCC CCACCGGCCG	900
AAGGCCTTAT TGGACGTGAC GATCAAGCTG GCCCCTCAT ACCGGGAGGA CACCAGCTGG	960
AAGAAGAGGT TGGCGGCCTC GGGCTCAAAC GGAATGTAAC CGACTTCGTC AACCACCAGG	1020
AGCGGATAGC GGCCAAACCG GGTGAGTTCG GCGTAGATGC GCCCGGCGTG GTGAGCCTCG	1080
GCGAACCGTG CTACCCATTC GGC GGCGGTG GCGAACAGCA CCCGATGACC GGCCTGACAC	1140
GCGCGTATCG CCAGGCCGAC CGCAAGATGA GTCTTCCCGG TGCCAGGCGG GGCCCAAAAA	1200
CACGACGTTA TCGCGGGCGG TGATGAAATC CAGGGTGCCC AGATGTGCGA TGGTGTCGCG	1260
TTTGAGGCCA CGAGCATGCT CAAAGTCGAA CTCTTCCAAC GACTTCCGAA CCGGGAAGCG	1320
GGCGGCGCGG ATGCGGCCCT CACCACCATG GGA CTCCCGG GCTGACACTT CCCGCTGCAG	1380
GCAGGCGGCC AGGTATTCTT CGTGGCTCCA GTTCTCGGCG CGGGCGCGAT CGGCCAGCCG	1440
GGAACTGAC TCACGCAGGG TGGGAGCTTT CAATGCTCTT GT	1482

## (2) INFORMATION FOR SEQ ID NO:19:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 876 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GAATTCGGCA CGAGCCGGCG ATAGCTTCTG GGCCGCGGCC GACCAGATGG CTCGAGGGTT	60
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CGTGCTCGGG GCCACGCGG GCGCACCAC CCTGACCGGT GAGGGCCTGC AACACGCCGA	120
CGGTCACTCG TTGCTGCTGG ACGCCACCAA CCCGGCGGTG GTTGCCTACG ACCCGGCCTT	180
CGCCTACGAA ATCGGCTACA TCGNGGAAAG CGGACTGGCC AGGATGTGCG GGGAGAACCC	240
GGAGAACATC TTCTTCTACA TCACCGTCTA CAACGAGCCG TACGTGCAGC CGCCGGAGCC	300
GGAGAACTTC GATCCCGAGG GCGTGCTGGG GGGTATCTAC CGNTATCAGC CGGCCACCGA	360
GCAACGCACC AACAAGGNGC AGATCCTGGC CTCCGGGGTA GCGATGCCCG CGGCGCTGCG	420
GGCAGCACAG ATGCTGGCCG CCGAGTGGGA TGTCGCCGCC GACGTGTGGT CGGTGACCAG	480
TTGGGGCGAG CTAAACGCG ACGGGGTGGT CATCGAGACC GAGAAGCTCC GCCACCCGA	540
TCGGCCGGCG GCGTGCCCT ACGTGACGAG AGCGCTGGAG AATGCTCGGG GCCCGGTGAT	600
CGCGGTGTCG GACTGGATGC GCGCGGTCCC CGAGCAGATC CGACCGTGGG TGCCGGGCAC	660
ATACCTCAG TTGGGCACCG ACGGGTTCGG TTTTCCGAC ACTCGGCCCG CCGGTCGTGC	720
TACTTCAAC ACCGACGCCG AATCCCAGGT TGGTCGCGGT TTTGGGAGGG GTTGGCCGGG	780
TCGACGGGTG AATATCGACC CATTCGGTGC CGGTCGTGGG CCGCCCGCCC AGTTACCCGG	840
ATTCGACGAA GGTGGGGGGT TCGCCCCGAN TAAGTT	876

## (2) INFORMATION FOR SEQ ID NO:20:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1021 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

ATCCCCCGG GCTGCAGGAA TTCGGCACGA GAGACAAAAT TCCACGCGTT AATGCAGGAA	60
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CAGATTCATA ACGAATTCAC AGCGGCACAA CAATATGTCG CGATCGCGGT TTATTTTCGAC	120
AGCGAAGACC TGCCGCAGTT GGCGAAGCAT TTTTACAGCC AAGCGGTCGA GGAACGAAAC	180
CATGCAATGA TGCTCGTGCA ACACCTGCTC GACCGCGACC TTCGTGTCGA AATTCCCAGC	240
GTAGACACGG TCGGAAACCA GTTCGACAGA CCCCAGGAGG CACTGGCGCT GGCCTCGAT	300
CAGGAACGCA CAGTCACCGA CCAGGTCGGT CGGCTGACAG CGGTGGCCCG CGACGAGGGC	360
GATTTCTTCG GCGAGCAGTT CATGCAGTGG TTCTTGACAG AACAGATCGA AGAGGTGGCC	420
TTGATGGCAA CCCTGGTGCG GGTTGCCGAT CGGGCCGGGG CCAACCTGTT CGAGCTAGAG	480
AACTTCGTCG CACGTGAAGT GGATGTGGCG CCGGCCGCAT CAGGCGCCCC GCACGCTGCC	540
GGGGGCCGCC TCTAGATCCC TGGGGGGGAT CAGCGAGTGG TCCCGTTCGC CCGCCCGTCT	600
TCCAGCCAGG CCTTGCTGCG GCCGGGGTGG TGAGTACCAA TCCAGGCCAC CCCGACCTCC	660
CGGNAAAAGT CGATGTCTC GTACTCATCG ACGTTCCAGG AGTACACCGC CCGGCCCTGA	720
GCTGCCGAGC GGTCAACGAG TTGCGGATAT TCCTTTAACG CAGGCAGTGA GGGTCCCACG	780
GCGGTTGGCC CGACCGCCGT GGCCGCACTG CTGGTCAGGT ATCGGGGGGT CTTGGCGAGC	840
AACAACGTCG GCAGGAGGGG TGGAGCCCGC CGGATCCGCA GACCGGGGGG GCGAAAACGA	900
CATCAACACC GCACGGGATC GATCTGCGGA GGGGGGTGCG GGAATACCGA ACCGGTGTAG	960
GAGCGCCAGC AGTTGTTTTT CCACCAGCGA AGCGTTTTCG GGTATCGGN GGCNNTTAAG	1020
T	1021

## (2) INFORMATION FOR SEQ ID NO:21:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 321 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CGTGCCGACG AACGGAAGAA CACAACCATG AAGATGGTGA AATCGATCGC CGCAGGTCTG	60
ACCGCCGCGG CTGCAATCGG CGCCGCTGCG GCCGGTGTGA CTTGATCAT GGCTGGCGGN	120
CCGGTCGTAT ACCAGATGCA GCCGGTCGTC TTCGGCGCGC CACTGCCGTT GGACCCGGNA	180
TCCGCCCTG ANGTCCCGAC CGCCGCCAG TGGACCAGNC TGCTCAACAG NCTCGNCGAT	240
CCCAACGTGT CGTTTGNGAA CAAGGGNAGT CTGGTCGAGG GNGGNATCGG NGGNANCGAG	300
GGNGNGNATC GNCGANACA A	321

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 373 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

TCTTATCGGT TCCGGTTGGC GACGGGTTTT GGGNGCGGGT GGTAAACCCG CTCGGCCAGC	60
CGATCGACGG GCGCGGAGAC GTCGACTCCG ATACTCGGCG CGCGCTGGAG CTCCAGGCGC	120
CCTCGGTGGT GNACCGGCAA GGCCTGAAGG AGCCGTTGNA GACCGGGATC AAGGCGATTG	180
ACGCGATGAC CCCGATCGGC CGCGGGCAGC GCCAGCTGAT CATCGGGGAC CGCAAGACCG	240
GCAAAAACCG CCGTCTGTGT CGGACACCAT CCTCAAACCA GCGGGAAGAA CTGGGAGTCC	300
GGTGGATCCC AAGAAGCAGG TCGCTTGTG TATACGTTGG CCATCGGGCA AGAAGGGGAA	360
CTTACCATCG CCG	373

(2) INFORMATION FOR SEQ ID NO:23:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 352 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GTGACGCCGT GATGGGATTC CTGGGCGGGG CCGGTCCGCT GCGGGTGGTG GATCAGCAAC	60
TGGTTACCCG GGTGCCGCAA GGCTGGTCGT TTGCTCAGGC AGCCGCTGTG CCGGTGGTGT	120
TCTTGACGGC CTGGTACGGG TTGGCCGATT TAGCCGAGAT CAAGGCGGGC GAATCGGTGC	180
TGATCCATGC CCGTACCGGC GGTGTGGGCA TGGCGGCTGT GCAGCTGGCT CGCCAGTGGG	240
GCGTGGAGGT TTTCGTCACC GCCAGCCGTG GNAAGTGGGA CACGCTGCGC GCCATNGNGT	300
TTGACGACGA NCCATATCGG NGATTCCNC ACATNCGAAG TTCCGANGGA GA	352

## (2) INFORMATION FOR SEQ ID NO:24:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 726 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GAAATCCGCG TTCATTCCGT TCGACCAGCG GCTGGCGATA ATCGACGAAG TGATCAAGCC	60
GCGGTTCGCG GCGCTCATGG GTCACAGCGA GTAATCAGCA AGTTCTCTGG TATATCGCAC	120
CTAGCGTCCA GTTGCTTGCC AGATCGCTTT CGTACCGTCA TCGCATGTAC CGGTTCGCGT	180
GCCGCACGCT CATGCTGGCG GCGTGCATCC TGGCCACGGG TGTGGCGGGT CTCGGGGTCG	240

GCGCGCAGTC CGCAGCCCAA ACCGCGCCGG TGCCCGACTA CTACTGGTGC CCGGGGCAGC	300
CTTTCGACCC CGCATGGGGG CCCAACTGGG ATCCCTACAC CTGCCATGAC GACTTCCACC	360
GCGACAGCGA CGGCCCCGAC CACAGCCGCG ACTACCCCGG ACCCATCCTC GAAGGTCCCG	420
TGCTTGACGA TCCCGGTGCT GCGCCGCCGC CCCC GGCTGC CGGTGGCGGC GCATAGCGCT	480
CGTTGACCGG GCCGCATCAG CGAATACGCG TATAAACCCG GGCGTGCCCC CGGCAAGCTA	540
CGACCCCCGG CGGGGCAGAT TTACGCTCCC GTGCCGATGG ATCGCGCCGT CCGATGACAG	600
AAAATAGGCG ACGGTTTTGG CAACCGCTTG GAGGACGCTT GAAGGGAACC TGTCATGAAC	660
GGCGACAGCG CCTCCACCAT CGACATCGAC AAGGTTGTTA CCCGCACACC CGTTCGCCGG	720
ATCGTG	726

## (2) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 580 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

CGCGACGACG ACGAACGTCG GGCCCACCAC CGCCTATGCG TTGATGCAGG CGACCGGGAT	60
GGTCGCCGAC CATATCCAAG CATGCTGGGT GCCCACTGAG CGACCTTTTG ACCAGCCGGG	120
CTGCCCCGATG GCGGCCCGGT GAAGTCATTG CGCCGGGGCT TGTGCACCTG ATGAACCCGA	180
ATAGGGAACA ATAGGGGGGT GATTTGGCAG TTCAATGTCG GGTATGGCTG GAAATCCAAT	240
GGCGGGGCAT GCTCGGCGCC GACCAGGCTC GCGCAGGCGG GCCAGCCCGA ATCTGGAGGG	300
AGCACTCAAT GGCGGCGATG AAGCCCCGGA CCGGCGACGG TCCTTTGGAA GCAACTAAGG	360

AGGGGCGCGG CATTGTGATG CGAGTACCAC TTGAGGGTGG CGGTCGCCTG GTCGTCGAGC	420
TGACACCCGA CGAAGCCGCC GCACTGGGTG ACGAACTCAA AGGCGTTACT AGCTAAGACC	480
AGCCCAACGG CGAATGGTCG GCGTTACGCG CACACCTTCC GGATAGATGTC CAGTGTCTGC	540
TCGGCGATGT ATGCCCAGGA GAACTCTTGG ATACAGCGCT	580

## (2) INFORMATION FOR SEQ ID NO:26:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 160 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

AACGGAGGCG CCGGGGGTTT TGGCGGGGCC GGGGCGGTG GCGGCAACGG CGGGGCCGGC	60
GGTACCGCCG GGTTGTTCCG TGTCGGCGGG GCCGGTGGGG CCGGAGGCAA CGGCATCGCC	120
GGTGTCACGG GTACGTCGGC CAGCACACCG GGTGGATCCG	160

## (2) INFORMATION FOR SEQ ID NO:27:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 272 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

GACACCGATA CGATGGTGAT GTACGCCAAC GTTGTCGACA CGCTCGAGGC GTTCACGATC	60
CAGCGCACAC CCGACGGCGT GACCATCGGC GATGCGGCCC CGTTCGCGGA GGCGGCTGCC	120

AAGGCGATGG GAATCGACAA GCTGCGGGTA ATTCATACCG GAATGGACCC CGTCGTCGCT	180
GAACGCGAAC AGTGGGACGA CGGCAACAAC ACGTTGGCGT TGGCGCCCGG TGTCGTTGTC	240
GCCTACGAGC GCAACGTACA GACCAACGCC CG	272

## (2) INFORMATION FOR SEQ ID NO:28:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 317 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GCAGCCGGTG GTTCTCGGAC TATCTGCGCA CGGTGACGCA GCGCGACGTG CGCGAGCTGA	60
AGCGGATCGA GCAGACGGAT CGCCTGCCGC GGTTCATGCG CTACCTGGCC GCTATCACCG	120
CGCAGGAGCT GAACGTGGCC GAAGCGGCGC GGGTCATCGG GGTGACGCG GGGACGATCC	180
GTTCGGATCT GGC GTGGTTC GAGACGGTCT ATCTGGTACA TCGCCTGCCC GCCTGGTCGC	240
GGAATCTGAC CGCGAAGATC AAGAAGCGGT CAAAGATCCA CGTCGTCGAC AGTGGCTTCG	300
CGGCCTGGTT GCGCGGG	317

## (2) INFORMATION FOR SEQ ID NO:29:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 182 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GATCGTGGAG CTGTGATGA ACAGCGTTGC CGGACGCGCG GCGGCCAGCA CGTCGGTGTA	60
GCAGCGCCGG ACCACCTCGC CGGTGGGCAG CATGGTGATG ACCACGTCGG CCTCGGCCAC	120
CGCTTCGGGC GCGCTACGAA ACACCGCGAC ACCGTGCGCG GCGGCGCCGG ACGCCGCCGT	180
GG	182

## (2) INFORMATION FOR SEQ ID NO:30:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 308 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GATCGCGAAG TTTGGTGAGC AGGTGGTCGA CGCGAAAGTC TGGGCGCCTG CGAAGCGGGT	60
CGGCGTTCAC GAGGCGAAGA CACGCCTGTC CGAGCTGCTG CGGCTCGTCT ACGGCGGGCA	120
GAGGTTGAGA TTGCCCCCGG CGGCGAGCCG GTAGCAAAGC TTGTGCCGCT GCATCCTCAT	180
GAGACTCGGC GGTTAGGCAT TGACCATGGC GTGTACCGCG TGCCCGACGA TTTGGACGCT	240
CCGTTGTCAG ACGACGTGCT CGAACGCTTT CACCGGTGAA GCGCTACCTC ATCGACACCC	300
ACGTTTGG	308

## (2) INFORMATION FOR SEQ ID NO:31:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 267 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

CCGACGACGA GCAACTCACG TGGATGATGG TCGGCAGCGG CATTGAGGAC GGAGAGAATC	60
CGGCCGAAGC TGCCGCGCGG CAAGTGCTCA TAGTGACCGG CCGTAGAGGG CTCCCCGAT	120
GGCACCGGAC TATTCTGGTG TGCCGCTGGC CGGTAAGAGC GGGTAAAAGA ATGTGAGGGG	180
ACACGATGAG CAATCACACC TACCGAGTGA TCGAGATCGT CGGGACCTCG CCCGACGGCG	240
TCGACGCGGC AATCCAGGGC GGTCTGG	267

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 189 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CTCGTGCCGA AAGAATGTGA GGGGACACGA TGAGCAATCA CACCTACCGA GTGATCGAGA	60
TCGTGCGGAC CTCGCCCCGAC GGCGTCGACG CGGCAATCCA GGGCGGTCTG GCCCCAGCTG	120
CGCAGACCAT GCGCGCGCTG GACTGGTTCG AAGTACAGTC AATTCGAGGC CACCTGGTCG	180
ACGGAGCGG	189

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 851 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CTGCAGGGTG GCGTGGATGA GCGTCACCGC GGGGCAGGCC GAGCTGACCG CCGCCCAGGT	60
CCGGGTTGCT GCGGCGGCCT ACGAGACGGC GTATGGGCTG ACGGTGCCCC CGCCGGTGAT	120
CGCCGAGAAC CGTGCTGAAC TGATGATTCT GATAGCGACC AACCTCTTGG GGCAAAACAC	180
CCCGGCGATC GCGGTCAACG AGGCCGAATA CGGCGAGATG TGGGCCCAAG ACGCCGCCGC	240
GATGTTTGGC TACGCCGCGG CGACGGCGAC GGCGACGGCG ACGTTGCTGC CGTTCGAGGA	300
GGCGCCGGAG ATGACCAGCG CGGGTGGGCT CCTCGAGCAG GCCGCCGCGG TCGAGGAGGC	360
CTCCGACACC GCCGCGGCGA ACCAGTTGAT GAACAATGTG CCCCAGGCGC TGAAACAGTT	420
GGCCCAGCCC ACGCAGGGCA CCACGCCTTC TTCCAAGCTG GGTGGCCTGT GGAAGACGGT	480
CTCGCCGCAT CGGTCGCCGA TCAGCAACAT GGTGTGCGATG GCCAACAACC ACATGTCGAT	540
GACCAACTCG GGTGTGTGCA TGACCAACAC CTTGAGCTCG ATGTTGAAGG GCTTTGCTCC	600
GGCGGCGGCC GCCCAGGCCG TGCAAACCGC GGCGCAAAAC GGGGTCCGGG CGATGAGCTC	660
GCTGGGCAGC TCGCTGGGTT CTTGGGTCT GGGCGGTGGG GTGGCCGCCA ACTTGGGTCG	720
GGCGGCCTCG GTACGGTATG GTCACCGGGA TGGCGGAAAA TATGCANAGT CTGGTCGGCG	780
GAACGGTGGT CCGGCGTAAG GTTTACCCCC GTTTTCTGGA TGCGGTGAAC TTCGTCAACG	840
GAAACAGTTA C	851

## (2) INFORMATION FOR SEQ ID NO:34:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 254 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GATCGATCGG GCGGAAATTT GGACCAGATT CGCCTCCGGC GATAACCCAA TCAATCGAAC	60
CTAGATTTAT TCGTCCAGG GGCCCGAGTA ATGGCTCGCA GGAGAGGAAC CTTACTGCTG	120
CGGGCACCTG TCGTAGGTCC TCGATACGGC GGAAGGCGTC GACATTTTCC ACCGACACCC	180
CCATCCAAAC GTTCGAGGGC CACTCCAGCT TGTGAGCGAG GCGACGCAGT CGCAGGCTGC	240
GCTTGGTCAA GATC	254

## (2) INFORMATION FOR SEQ ID NO:35:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 408 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

CGGCACGAGG ATCCTGACCG AAGCGGCCGC CGCCAAGGCG AAGTCGCTGT TGGACCAGGA	60
GGGACGGGAC GATCTGGCGC TCGGATCGC GGTTCAGCCG GGGGGGTGCG CTGGATTGCG	120
CTATAACCTT TTCTTCGACG ACCGGACGCT GGATGGTGAC CAAACGCGG AGTTCGGTGG	180
TGTCAGGTTG ATCGTGGACC GGATGAGCGC GCCGTATGTG GAAGGCGCGT CGATCGATTT	240
CGTCGACACT ATTGAGAAGC AAGGNTTCAC CATCGACAAT CCCAACGCCA CCGGCTCCTG	300
CGCGTGCGGG GATTCGTTCA ACTGATAAAA CGCTAGTACG ACCCCGCGGT GCGCAACACG	360
TACGAGCACA CCAAGACCTG ACCGCGCTGG AAAAGCAACT GAGCGATG	408

## (2) INFORMATION FOR SEQ ID NO:36:

## (i) SEQUENCE CHARACTERISTICS:

78

- (A) LENGTH: 181 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GCGGTGTCGG CGGATCCGGC GGGTGGTTGA ACGGCAACGG CGGGGCCGGC GGGGCCGGCG	60
GGACCGGGCG TAACGGTGGT GCCGGCGGCA ACGCCTGGTT GTTCGGGGCC GGCGGGTCCG	120
GCGGNGCCGG CACCAATGGT GGNGTCGGCG GTCCGGCGG ATTTGTCTAC GGCAACGGCG	180
G	181

## (2) INFORMATION FOR SEQ ID NO:37:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 290 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

GCGGTGTCGG CGGATCCGGC GGGTGGTTGA ACGGCAACGG CGGTGTCGGC GGCCGGGGCG	60
GCGACGGCGT CTTTGCCGGT GCCGGCGGCC AGGGCGGCCT CGGTGGGCAG GGCGGCAATG	120
GCGGCGGCTC CACCGGCGGC AACGGCGGTC TTGGCGGCGC GGGCGGTGGC GGAGGCAACG	180
CCCCGGACGG CGGCTTCGGT GGCAACGGCG GTAAGGGTGG CCAGGGCGGN ATTGGCGGCG	240
GCACTCAGAG CGCGACCGGC CTCGGNGGTG ACGGCGGTGA CGGCGGTGAC	290

## (2) INFORMATION FOR SEQ ID NO:38:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 34 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

GATCCAGTGG CATGGNGGGT GTCAGTGGAA GCAT

34

(2) INFORMATION FOR SEQ ID NO:39:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 155 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

GATCGCTGCT CGTCCCCCCC TTGCCGCCGA CGCCACCGGT CCCACCGTTA CCGAACAAGC 60

TGGCGTGGTC GCCAGCACCC CCGGCACCGC CGACGCCGGA GTCGAACAAT GGCACCGTCG 120

TATCCCCACC ATTGCCGCCG GNCCCACCGG CACCG 155

(2) INFORMATION FOR SEQ ID NO:40:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 53 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

ATGGCGTTCA CGGGGCGCCG GGGACCGGGC AGCCCGGNGG GGCCGGGGGG TGG 53

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 132 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

GATCCACCGC GGGTGCAGAC GGTGCCC GCGCCACCCC GACCAGCGGC GGCAACGGCG 60  
 GCACCGGCGG CAACGGCGCG AACGCCACCG TCGTCGGNGG GGCCGGCGGG GCCGGCGGCA 120  
 AGGGCGGCAA CG 132

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 132 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

GATCGGCGGC CGGNACGGNC GGGGACGGCG GCAAGGGCGG NAACGGGGGC GCCGNAGCCA 60  
 CCNGCCAAGA ATCCTCCNG TCCNCCAATG GCGCGAATGG CGGACAGGGC GGCAACGGCG 120  
 GCANCGGCGG CA 132

## (2) INFORMATION FOR SEQ ID NO:43:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 702 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CGGCACGAGG ATCGGTACCC CGCGGCATCG GCAGCTGCCG ATTCGCCGGG TTTCCCACC	60
CGAGGAAAGC CGCTACCAGA TGGCGTGCC GAAGTAGGGC GATCCGTTCC CGATGCCGGC	120
ATGAACGGGC GGCATCAAAT TAGTGAGGA ACCTTTCAGT TTAGCGACGA TAATGGCTAT	180
AGCACTAAGG AGGATGATCC GATATGACGC AGTCGCAGAC CGTGACGGTG GATCAGCAAG	240
AGATTTTGAA CAGGGCCAAC GAGGTGGAGG CCCCAGTGGC GGACCCACCG ACTGATGTCC	300
CCATCACACC GTGCGAACTC ACGGNGGNTA AAAACGCCGC CCAACAGNTG GTNTTGTCCG	360
CCGACAACAT GCGGGAATAC CTGGCGGCCG GTGCCAAAGA GCGGCAGCGT CTGGCGACCT	420
CGCTGCGCAA CGCGGCCAAG GNGTATGGCG AGGTTGATGA GGAGGCTGCG ACCGCGCTGG	480
ACAACGACGG CGAAGGAACT GTGCAGGCAG AATCGGCCGG GGCCGTCGGA GGGGACAGTT	540
CGGCCGAACT AACCGATACG CCGAGGGTGG CCACGGCCGG TGAACCCAAC TTCATGGATC	600
TCAAAGAAGC GGCAAGGAAG CTCGAAACGG GCGACCAAGG CGCATCGCTC GCGCACTGNG	660
GGGATGGGTG GAACACTTNC ACCCTGACGC TGCAAGGCCA CG	702

## (2) INFORMATION FOR SEQ ID NO:44:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 298 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

GAAGCCGCAG CGCTGTCGGG CGACGTGGCG GTCAAAGCGG CATCGCTCGG TGGCGGTGGA	60
GGCGGCGGGG TGCCGTCGGC GCCGTTGGGA TCCGCGATCG GGGGCGCCGA ATCGGTGCGG	120
CCCGCTGGCG CTGGTGACAT TGCCGGCTTA GGCCAGGGAA GGGCCGGCGG CGGCGCCGCG	180
CTGGGCGGCG GTGGCATGGG AATGCCGATG GGTGCCGCGC ATCAGGGACA AGGGGGCGCC	240
AAGTCCAAGG GTTCTCAGCA GGAAGACGAG GCGCTCTACA CCGAGGATCC TCGTGCCG	298

## (2) INFORMATION FOR SEQ ID NO:45:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1058 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CGGCACGAGG ATCGAATCGC GTCGCCGGGA GCACAGCGTC GCACTGCACC AGTGGAGGAG	60
CCATGACCTA CTCGCCGGGT AACCCCGGAT ACCCGCAAGC GCAGCCCGCA GGCTCCTACG	120
GAGGCGTCAC ACCCTCGTTC GCCCAGCCG ATGAGGGTGC GAGCAAGCTA CCGATGTACC	180
TGAACATCGC GGTGGCAGTG CTCGGTCTGG CTGCGTACTT CGCCAGCTTC GGCCCAATGT	240
TCACCCTCAG TACCGAACTC GGGGGGGGTG ATGGCGCAGT GTCCGGTGAC ACTGGGCTGC	300
CGGTCGGGGT GGCTCTGCTG GCTGCGCTGC TTGCCGGGGT GGTCTGGTG CCTAAGGCCA	360
AGAGCCATGT GACGGTAGTT GCGGTGCTCG GGGTACTCGG CGTATTCTG ATGGTCTCGG	420

CGACGTTTAA CAAGCCCAGC GCCTATTCGA CCGGTTGGGC ATTGTGGGTT GTGTTGGCTT	480
TCATCGTGTT CCAGGCGGTT GCGGCAGTCC TGGCGCTCTT GGTGGAGACC GGCGCTATCA	540
CCGCGCCGGC GCCGCGGCC AAGTTCGACC CGTATGGACA GTACGGGCGG TACGGGCAGT	600
ACGGGCAGTA CGGGGTGCAG CCGGGTGGGT ACTACGGTCA GCAGGGTGCT CAGCAGGCCG	660
CGGGACTGCA GTCGCCCCGC CCGCAGCAGT CTCCGAGCC TCCCGGATAT GGGTCGCAGT	720
ACGGCGGCTA TTCGTCCAGT CCGAGCCAAT CGGGCAGTGG ATACACTGCT CAGCCCCCGG	780
CCCAGCCGCC GGCGCAGTCC GGGTCGCAAC AATCGCACCA GGGCCCATCC ACGCCACCTA	840
CCGGCTTTCC GAGCTTCAGC CCACCACCAC CGGTCAGTGC CGGGACGGGG TCGCAGGCTG	900
GTTGGGCTCC AGTCAACTAT TCAAACCCCA GCGGGGGCGA GCAGTCGTCG TCCCCGGGG	960
GGGCGCCGGT CTAACCGGGC GTTCCCGCGT CCGGTCGCGC GTGTGCGCGA AGAGTGAACA	1020
GGGTGTCAGC AAGCGCGGAC GATCCTCGTG CCGAATTC	1058

## (2) INFORMATION FOR SEQ ID NO:46:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 327 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

CGGCACGAGA GACCGATGCC GCTACCCTCG CGCAGGAGGC AGGTAATTTT GAGCGGATCT	60
CCGGCGACCT GAAAACCCAG ATCGACCAGG TGGAGTCGAC GGCAGGTTCT TTGCAGGGCC	120
AGTGGCGCGG CGCGGCGGGG ACGGCCGCCC AGGCCGCGGT GGTGCGCTTC CAAGAAGCAG	180
CCAATAAGCA GAAGCAGGAA CTCGACGAGA TCTCGACGAA TATTCGTCAG GCCGGCGTCC	240
AATACTCGAG GGCCGACGAG GAGCAGCAGC AGGCGCTGTC CTCGCAAATG GGCTTCTGAC	300

CCGCTAATAC GAAAAGAAAC GGAGCAA

327

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 170 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

CGGTCGCGAT GATGGCGTTG TCGAACGTGA CCGATTCTGT ACCGCCGTCG TTGAGATCAA 60

CCAACAACGT GTTGGCGTCG GCAAATGTGC CGNACCCGTG GATCTCGGTG ATCTTGTCT 120

TCTTCATCAG GAAGTGCACA CCGGCCACCC TGCCCTCGGN TACCTTTCGG 170

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 127 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GATCCGGCGG CACGGGGGGT GCCGGCGGCA GCACCGCTGG CGCTGGCGGC AACGGCGGGG 60

CCGGGGGTGG CGGCGGAACC GGTGGGTTGC TCTTCGGCAA CGGCGGTGCC GGCGGGCACG 120

GGGCCGT 127

(2) INFORMATION FOR SEQ ID NO:49:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 81 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

CGGCGGCAAG GGC GG CACCG CCGGCAACGG GAGCGGCGCG GCCGGCGGCA ACGGCGGCAA	60
CGGCGGCTCC GGCCTCAACG G	81

(2) INFORMATION FOR SEQ ID NO:50:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 149 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

GATCAGGGCT GGCCGGCTCC GGCCAGAAGG GCGGTAACGG AGGAGCTGCC GGATTGTTTG	60
GCAACGGCGG GGCCGGNGGT GCCGGCGCGT CCAACCAAGC CGGTAACGGC GGNGCCGGCG	120
GAAACGGTGG TGCCGGTGGG CTGATCTGG	149

(2) INFORMATION FOR SEQ ID NO:51:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 355 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

CGGCACGAGA TCACACCTAC CGAGTGATCG AGATCGTCGG GACCTCGCCC GACGGTGTCTG	60
ACGCGGNAAT CCAGGGCGGT CTGGCCCGAG CTGCGCAGAC CATGCGCGCG CTGGACTGGT	120
TCGAAGTACA GTCAATTCGA GGCCACCTGG TCGACGGAGC GGTCGCGCAC TTCCAGGTGA	180
CTATGAAAGT CGGCTTCCGC CTGGAGGATT CCTGAACCTT CAAGCGCGGC CGATAACTGA	240
GGTGCATCAT TAAGCGACTT TTCCAGAACA TCCTGACGCG CTCGAAACGC GGTTCAGCCG	300
ACGGTGGCTC CGCCGAGGCG CTGCCTCAA AATCCCTGCG ACAATTCGTC GGC GG	355

## (2) INFORMATION FOR SEQ ID NO:52:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 999 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

ATGCATCACC ATCACCATCA CATGCATCAG GTGGACCCCA ACTTGACACG TCGCAAGGGA	60
CGATTGGCGG CACTGGCTAT CGCGGCGATG GCCAGCGCCA GCCTGGTGAC CGTTGCGGTG	120
CCCGCGACCG CCAACGCCGA TCCGGAGCCA GCGCCCCCGG TACCCACAAC GGCCGCCTCG	180
CCGCCGTCTGA CCGCTGCAGC GCCACCCGCA CCGGCGACAC CTGTTGCCCC CCCACCACCG	240
GCCGCCGCCA ACACGCCGAA TGCCCAGCCG GGCGATCCCA ACGCAGCACC TCCGCCGGCC	300
GACCCGAACG CACCGCCGCC ACCTGTCATT GCCCAAACG CACCCCAACC TGTCCGGATC	360
GACAACCCGG TTGGAGGATT CAGCTTCGCG CTGCCTGCTG GCTGGGTGGA GTCTGACGCC	420

GCCCACTTCG ACTACGGTTC AGCACTCCTC AGCAAAACCA CCGGGGACCC GCCATTTCCC 480  
 GGACAGCCGC CGCCGGTGGC CAATGACACC CGTATCGTGC TCGGCCGGCT AGACCAAAG 540  
 CTTTACGCCA GCGCCGAAGC CACCGACTCC AAGGCCGCGG CCCGGTTGGG CTCGGACATG 600  
 GGTGAGTTCT ATATGCCCTA CCCGGGCACC CGGATCAACC AGGAAACCGT CTCGCTCGAC 660  
 GCCAACGGGG TGTCTGGAAG CGCGTCGTAT TACGAAGTCA AGTTCAGCGA TCCGAGTAAG 720  
 CCGAACGGCC AGATCTGGAC GGGCGTAATC GGCTCGCCCG CGGCGAACGC ACCGGACGCC 780  
 GGGCCCCCTC AGCGCTGGTT TGTGGTATGG CTCGGGACCG CCAACAACCC GGTGGACAAG 840  
 GGCGCGGCCA AGGCGCTGGC CGAATCGATC CGGCCTTTGG TCGCCCCGCC GCCGGCGCCG 900  
 GCACCGGCTC CTGCAGAGCC CGCTCCGGCG CCGGCGCCGG CCGGGGAAGT CGCTCCTACC 960  
 CCGACGACAC CGACACCGCA GCGGACCTTA CCGGCCTGA 999

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 332 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Met	His	His	His	His	His	His	Met	His	Gln	Val	Asp	Pro	Asn	Leu	Thr
1				5					10					15	
Arg	Arg	Lys	Gly	Arg	Leu	Ala	Ala	Leu	Ala	Ile	Ala	Ala	Met	Ala	Ser
			20					25					30		
Ala	Ser	Leu	Val	Thr	Val	Ala	Val	Pro	Ala	Thr	Ala	Asn	Ala	Asp	Pro
		35					40					45			
Glu	Pro	Ala	Pro	Pro	Val	Pro	Thr	Thr	Ala	Ala	Ser	Pro	Pro	Ser	Thr
	50					55					60				

Ala Ala Ala Pro Pro Ala Pro Ala Thr Pro Val Ala Pro Pro Pro Pro  
 65 70 75 80  
 Ala Ala Ala Asn Thr Pro Asn Ala Gln Pro Gly Asp Pro Asn Ala Ala  
 85 90 95  
 Pro Pro Pro Ala Asp Pro Asn Ala Pro Pro Pro Pro Val Ile Ala Pro  
 100 105 110  
 Asn Ala Pro Gln Pro Val Arg Ile Asp Asn Pro Val Gly Gly Phe Ser  
 115 120 125  
 Phe Ala Leu Pro Ala Gly Trp Val Glu Ser Asp Ala Ala His Phe Asp  
 130 135 140  
 Tyr Gly Ser Ala Leu Leu Ser Lys Thr Thr Gly Asp Pro Pro Phe Pro  
 145 150 155 160  
 Gly Gln Pro Pro Pro Val Ala Asn Asp Thr Arg Ile Val Leu Gly Arg  
 165 170 175  
 Leu Asp Gln Lys Leu Tyr Ala Ser Ala Glu Ala Thr Asp Ser Lys Ala  
 180 185 190  
 Ala Ala Arg Leu Gly Ser Asp Met Gly Glu Phe Tyr Met Pro Tyr Pro  
 195 200 205  
 Gly Thr Arg Ile Asn Gln Glu Thr Val Ser Leu Asp Ala Asn Gly Val  
 210 215 220  
 Ser Gly Ser Ala Ser Tyr Tyr Glu Val Lys Phe Ser Asp Pro Ser Lys  
 225 230 235 240  
 Pro Asn Gly Gln Ile Trp Thr Gly Val Ile Gly Ser Pro Ala Ala Asn  
 245 250 255  
 Ala Pro Asp Ala Gly Pro Pro Gln Arg Trp Phe Val Val Trp Leu Gly  
 260 265 270  
 Thr Ala Asn Asn Pro Val Asp Lys Gly Ala Ala Lys Ala Leu Ala Glu  
 275 280 285  
 Ser Ile Arg Pro Leu Val Ala Pro Pro Pro Ala Pro Ala Pro Ala Pro  
 290 295 300

Ala Glu Pro Ala Pro Ala Pro Ala Pro Ala Gly Glu Val Ala Pro Thr  
 305 310 315 320

Pro Thr Thr Pro Thr Pro Gln Arg Thr Leu Pro Ala  
 325 330

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Asp Pro Val Asp Ala Val Ile Asn Thr Thr Xaa Asn Tyr Gly Gln Val  
 1 5 10 15

Val Ala Ala Leu  
 20

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Ala Val Glu Ser Gly Met Leu Ala Leu Gly Thr Pro Ala Pro Ser  
 1 5 10 15

(2) INFORMATION FOR SEQ ID NO:56:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 19 amino acids  
    (B) TYPE: amino acid  
    (C) STRANDEDNESS:  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Ala Ala Met Lys Pro Arg Thr Gly Asp Gly Pro Leu Glu Ala Ala Lys  
1                    5                    10                    15  
Glu Gly Arg

(2) INFORMATION FOR SEQ ID NO:57:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 15 amino acids  
    (B) TYPE: amino acid  
    (C) STRANDEDNESS:  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

Tyr Tyr Trp Cys Pro Gly Gln Pro Phe Asp Pro Ala Trp Gly Pro  
1                    5                    10                    15

(2) INFORMATION FOR SEQ ID NO:58:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 14 amino acids  
    (B) TYPE: amino acid  
    (C) STRANDEDNESS:  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

Asp Ile Gly Ser Glu Ser Thr Glu Asp Gln Gln Xaa Ala Val  
1                      5                      10

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 13 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

Ala Glu Glu Ser Ile Ser Thr Xaa Glu Xaa Ile Val Pro  
1                      5                      10

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Asp Pro Glu Pro Ala Pro Pro Val Pro Thr Ala Ala Ala Ala Pro Pro  
1                      5                      10                      15

Ala

## (2) INFORMATION FOR SEQ ID NO:61:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

Ala	Pro	Lys	Thr	Tyr	Xaa	Glu	Glu	Leu	Lys	Gly	Thr	Asp	Thr	Gly
1				5					10					15

## (2) INFORMATION FOR SEQ ID NO:62:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Asp	Pro	Ala	Ser	Ala	Pro	Asp	Val	Pro	Thr	Ala	Ala	Gln	Gln	Thr	Ser
1				5					10					15	
Leu	Leu	Asn	Asn	Leu	Ala	Asp	Pro	Asp	Val	Ser	Phe	Ala	Asp		
		20						25					30		

## (2) INFORMATION FOR SEQ ID NO:63:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 187 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

Thr	Gly	Ser	Leu	Asn	Gln	Thr	His	Asn	Arg	Arg	Ala	Asn	Glu	Arg	Lys	
1				5					10					15		
Asn	Thr	Thr	Met	Lys	Met	Val	Lys	Ser	Ile	Ala	Ala	Gly	Leu	Thr	Ala	
			20					25					30			
Ala	Ala	Ala	Ile	Gly	Ala	Ala	Ala	Ala	Gly	Val	Thr	Ser	Ile	Met	Ala	
		35				40						45				
Gly	Gly	Pro	Val	Val	Tyr	Gln	Met	Gln	Pro	Val	Val	Phe	Gly	Ala	Pro	
	50					55					60					
Leu	Pro	Leu	Asp	Pro	Ala	Ser	Ala	Pro	Asp	Val	Pro	Thr	Ala	Ala	Gln	
65					70					75					80	
Leu	Thr	Ser	Leu	Leu	Asn	Ser	Leu	Ala	Asp	Pro	Asn	Val	Ser	Phe	Ala	
			85						90					95		
Asn	Lys	Gly	Ser	Leu	Val	Glu	Gly	Gly	Ile	Gly	Gly	Thr	Glu	Ala	Arg	
			100					105					110			
Ile	Ala	Asp	His	Lys	Leu	Lys	Lys	Ala	Ala	Glu	His	Gly	Asp	Leu	Pro	
		115					120					125				
Leu	Ser	Phe	Ser	Val	Thr	Asn	Ile	Gln	Pro	Ala	Ala	Ala	Gly	Ser	Ala	
	130					135					140					
Thr	Ala	Asp	Val	Ser	Val	Ser	Gly	Pro	Lys	Leu	Ser	Ser	Pro	Val	Thr	
145					150					155					160	
Gln	Asn	Val	Thr	Phe	Val	Asn	Gln	Gly	Gly	Trp	Met	Leu	Ser	Arg	Ala	
				165					170					175		
Ser	Ala	Met	Glu	Leu	Leu	Gln	Ala	Ala	Gly	Xaa						
			180					185								

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:

94

- (A) LENGTH: 148 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

```

Asp Glu Val Thr Val Glu Thr Thr Ser Val Phe Arg Ala Asp Phe Leu
1           5           10           15
Ser Glu Leu Asp Ala Pro Ala Gln Ala Gly Thr Glu Ser Ala Val Ser
          20           25           30
Gly Val Glu Gly Leu Pro Pro Gly Ser Ala Leu Leu Val Val Lys Arg
          35           40           45
Gly Pro Asn Ala Gly Ser Arg Phe Leu Leu Asp Gln Ala Ile Thr Ser
          50           55           60
Ala Gly Arg His Pro Asp Ser Asp Ile Phe Leu Asp Asp Val Thr Val
65           70           75           80
Ser Arg Arg His Ala Glu Phe Arg Leu Glu Asn Asn Glu Phe Asn Val
          85           90           95
Val Asp Val Gly Ser Leu Asn Gly Thr Tyr Val Asn Arg Glu Pro Val
          100          105          110
Asp Ser Ala Val Leu Ala Asn Gly Asp Glu Val Gln Ile Gly Lys Leu
          115          120          125
Arg Leu Val Phe Leu Thr Gly Pro Lys Gln Gly Glu Asp Asp Gly Ser
          130          135          140
Thr Gly Gly Pro
          145

```

## (2) INFORMATION FOR SEQ ID NO:65:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 230 amino acids

(B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

Thr	Ser	Asn	Arg	Pro	Ala	Arg	Arg	Gly	Arg	Arg	Ala	Pro	Arg	Asp	Thr
1				5				10						15	
Gly	Pro	Asp	Arg	Ser	Ala	Ser	Leu	Ser	Leu	Val	Arg	His	Arg	Arg	Gln
			20				25						30		
Gln	Arg	Asp	Ala	Leu	Cys	Leu	Ser	Ser	Thr	Gln	Ile	Ser	Arg	Gln	Ser
		35					40						45		
Asn	Leu	Pro	Pro	Ala	Ala	Gly	Gly	Ala	Ala	Asn	Tyr	Ser	Arg	Arg	Asn
	50					55					60				
Phe	Asp	Val	Arg	Ile	Lys	Ile	Phe	Met	Leu	Val	Thr	Ala	Val	Val	Leu
65					70					75					80
Leu	Cys	Cys	Ser	Gly	Val	Ala	Thr	Ala	Ala	Pro	Lys	Thr	Tyr	Cys	Glu
				85					90					95	
Glu	Leu	Lys	Gly	Thr	Asp	Thr	Gly	Gln	Ala	Cys	Gln	Ile	Gln	Met	Ser
			100					105					110		
Asp	Pro	Ala	Tyr	Asn	Ile	Asn	Ile	Ser	Leu	Pro	Ser	Tyr	Tyr	Pro	Asp
		115					120					125			
Gln	Lys	Ser	Leu	Glu	Asn	Tyr	Ile	Ala	Gln	Thr	Arg	Asp	Lys	Phe	Leu
	130					135					140				
Ser	Ala	Ala	Thr	Ser	Ser	Thr	Pro	Arg	Glu	Ala	Pro	Tyr	Glu	Leu	Asn
145					150					155					160
Ile	Thr	Ser	Ala	Thr	Tyr	Gln	Ser	Ala	Ile	Pro	Pro	Arg	Gly	Thr	Gln
				165					170					175	
Ala	Val	Val	Leu	Xaa	Val	Tyr	His	Asn	Ala	Gly	Gly	Thr	His	Pro	Thr
			180					185					190		

Thr Thr Tyr Lys Ala Phe Asp Trp Asp Gln Ala Tyr Arg Lys Pro Ile  
 195 200 205

Thr Tyr Asp Thr Leu Trp Gln Ala Asp Thr Asp Pro Leu Pro Val Val  
 210 215 220

Phe Pro Ile Val Ala Arg  
 225 230

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 132 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe  
 1 5 10 15

Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser  
 20 25 30

Gly Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly  
 35 40 45

Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val  
 50 55 60

Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val  
 65 70 75 80

Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala  
 85 90 95

Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp  
 100 105 110

97

Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu  
 115 120 125

Gly Pro Pro Ala  
 130

## (2) INFORMATION FOR SEQ ID NO:67:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 100 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

Val Pro Leu Arg Ser Pro Ser Met Ser Pro Ser Lys Cys Leu Ala Ala  
 1 5 10 15

Ala Gln Arg Asn Pro Val Ile Arg Arg Arg Arg Leu Ser Asn Pro Pro  
 20 25 30

Pro Arg Lys Tyr Arg Ser Met Pro Ser Pro Ala Thr Ala Ser Ala Gly  
 35 40 45

Met Ala Arg Val Arg Arg Arg Ala Ile Trp Arg Gly Pro Ala Thr Xaa  
 50 55 60

Ser Ala Gly Met Ala Arg Val Arg Arg Trp Xaa Val Met Pro Xaa Val  
 65 70 75 80

Ile Gln Ser Thr Xaa Ile Arg Xaa Xaa Gly Pro Phe Asp Asn Arg Gly  
 85 90 95

Ser Glu Arg Lys  
 100

## (2) INFORMATION FOR SEQ ID NO:68:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 163 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (Q) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

```

Met Thr Asp Asp Ile Leu Leu Ile Asp Thr Asp Glu Arg Val Arg Thr
1           5           10           15
Leu Thr Leu Asn Arg Pro Gln Ser Arg Asn Ala Leu Ser Ala Ala Leu
20           25           30
Arg Asp Arg Phe Phe Ala Xaa Leu Xaa Asp Ala Glu Xaa Asp Asp Asp
35           40           45
Ile Asp Val Val Ile Leu Thr Gly Ala Asp Pro Val Phe Cys Ala Gly
50           55           60
Leu Asp Leu Lys Val Ala Gly Arg Ala Asp Arg Ala Ala Gly His Leu
65           70           75           80
Thr Ala Val Gly Gly His Asp Gln Ala Gly Asp Arg Arg Asp Gln Arg
85           90           95
Arg Arg Gly His Arg Arg Ala Arg Thr Gly Ala Val Leu Arg His Pro
100          105          110
Asp Arg Leu Arg Ala Arg Pro Leu Arg Arg His Pro Arg Pro Gly Gly
115          120          125
Ala Ala Ala His Leu Gly Thr Gln Cys Val Leu Ala Ala Lys Gly Arg
130          135          140
His Arg Xaa Gly Pro Val Asp Glu Pro Asp Arg Arg Leu Pro Val Arg
145          150          155          160
Asp Arg Arg

```

(2) INFORMATION FOR SEQ ID NO:69:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 344 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

```

Met Lys Phe Val Asn His Ile Glu Pro Val Ala Pro Arg Arg Ala Gly
1           5           10           15
Gly Ala Val Ala Glu Val Tyr Ala Glu Ala Arg Arg Glu Phe Gly Arg
          20           25           30
Leu Pro Glu Pro Leu Ala Met Leu Ser Pro Asp Glu Gly Leu Leu Thr
          35           40           45
Ala Gly Trp Ala Thr Leu Arg Glu Thr Leu Leu Val Gly Gln Val Pro
          50           55           60
Arg Gly Arg Lys Glu Ala Val Ala Ala Ala Val Ala Ala Ser Leu Arg
65           70           75           80
Cys Pro Trp Cys Val Asp Ala His Thr Thr Met Leu Tyr Ala Ala Gly
          85           90           95
Gln Thr Asp Thr Ala Ala Ala Ile Leu Ala Gly Thr Ala Pro Ala Ala
          100          105          110
Gly Asp Pro Asn Ala Pro Tyr Val Ala Trp Ala Ala Gly Thr Gly Thr
          115          120          125
Pro Ala Gly Pro Pro Ala Pro Phe Gly Pro Asp Val Ala Ala Glu Tyr
          130          135          140
Leu Gly Thr Ala Val Gln Phe His Phe Ile Ala Arg Leu Val Leu Val
145          150          155          160
Leu Leu Asp Glu Thr Phe Leu Pro Gly Gly Pro Arg Ala Gln Gln Leu
          165          170          175

```

100

Met Arg Arg Ala Gly Gly Leu Val Phe Ala Arg Lys Val Arg Ala Glu  
 180 185 190  
 His Arg Pro Gly Arg Ser Thr Arg Arg Leu Glu Pro Arg Thr Leu Pro  
 195 200 205  
 Asp Asp Leu Ala Trp Ala Thr Pro Ser Glu Pro Ile Ala Thr Ala Phe  
 210 215 220  
 Ala Ala Leu Ser His His Leu Asp Thr Ala Pro His Leu Pro Pro Pro  
 225 230 235 240  
 Thr Arg Gln Val Val Arg Arg Val Val Gly Ser Trp His Gly Glu Pro  
 245 250 255  
 Met Pro Met Ser Ser Arg Trp Thr Asn Glu His Thr Ala Glu Leu Pro  
 260 265 270  
 Ala Asp Leu His Ala Pro Thr Arg Leu Ala Leu Leu Thr Gly Leu Ala  
 275 280 285  
 Pro His Gln Val Thr Asp Asp Asp Val Ala Ala Ala Arg Ser Leu Leu  
 290 295 300  
 Asp Thr Asp Ala Ala Leu Val Gly Ala Leu Ala Trp Ala Ala Phe Thr  
 305 310 315 320  
 Ala Ala Arg Arg Ile Gly Thr Trp Ile Gly Ala Ala Ala Glu Gly Gln  
 325 330 335  
 Val Ser Arg Gln Asn Pro Thr Gly  
 340

## (2) INFORMATION FOR SEQ ID NO:70:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 485 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

Asp	Asp	Pro	Asp	Met	Pro	Gly	Thr	Val	Ala	Lys	Ala	Val	Ala	Asp	Ala	1	5	10	15
Leu	Gly	Arg	Gly	Ile	Ala	Pro	Val	Glu	Asp	Ile	Gln	Asp	Cys	Val	Glu	20	25	30	
Ala	Arg	Leu	Gly	Glu	Ala	Gly	Leu	Asp	Asp	Val	Ala	Arg	Val	Tyr	Ile	35	40	45	
Ile	Tyr	Arg	Gln	Arg	Arg	Ala	Glu	Leu	Arg	Thr	Ala	Lys	Ala	Leu	Leu	50	55	60	
Gly	Val	Arg	Asp	Glu	Leu	Lys	Leu	Ser	Leu	Ala	Ala	Val	Thr	Val	Leu	65	70	75	80
Arg	Glu	Arg	Tyr	Leu	Leu	His	Asp	Glu	Gln	Gly	Arg	Pro	Ala	Glu	Ser	85	90	95	
Thr	Gly	Glu	Leu	Met	Asp	Arg	Ser	Ala	Arg	Cys	Val	Ala	Ala	Ala	Glu	100	105	110	
Asp	Gln	Tyr	Glu	Pro	Gly	Ser	Ser	Arg	Arg	Trp	Ala	Glu	Arg	Phe	Ala	115	120	125	
Thr	Leu	Leu	Arg	Asn	Leu	Glu	Phe	Leu	Pro	Asn	Ser	Pro	Thr	Leu	Met	130	135	140	
Asn	Ser	Gly	Thr	Asp	Leu	Gly	Leu	Leu	Ala	Gly	Cys	Phe	Val	Leu	Pro	145	150	155	160
Ile	Glu	Asp	Ser	Leu	Gln	Ser	Ile	Phe	Ala	Thr	Leu	Gly	Gln	Ala	Ala	165	170	175	
Glu	Leu	Gln	Arg	Ala	Gly	Gly	Gly	Thr	Gly	Tyr	Ala	Phe	Ser	His	Leu	180	185	190	
Arg	Pro	Ala	Gly	Asp	Arg	Val	Ala	Ser	Thr	Gly	Gly	Thr	Ala	Ser	Gly	195	200	205	
Pro	Val	Ser	Phe	Leu	Arg	Leu	Tyr	Asp	Ser	Ala	Ala	Gly	Val	Val	Ser	210	215	220	

102

Met Gly Gly Arg Arg Arg Gly Ala Cys Met Ala Val Leu Asp Val Ser  
 225 230 235 240  
 His Pro Asp Ile Cys Asp Phe Val Thr Ala Lys Ala Glu Ser Pro Ser  
 245 250 255  
 Glu Leu Pro His Phe Asn Leu Ser Val Gly Val Thr Asp Ala Phe Leu  
 260 265 270  
 Arg Ala Val Glu Arg Asn Gly Leu His Arg Leu Val Asn Pro Arg Thr  
 275 280 285  
 Gly Lys Ile Val Ala Arg Met Pro Ala Ala Glu Leu Phe Asp Ala Ile  
 290 295 300  
 Cys Lys Ala Ala His Ala Gly Gly Asp Pro Gly Leu Val Phe Leu Asp  
 305 310 315 320  
 Thr Ile Asn Arg Ala Asn Pro Val Pro Gly Arg Gly Arg Ile Glu Ala  
 325 330 335  
 Thr Asn Pro Cys Gly Glu Val Pro Leu Leu Pro Tyr Glu Ser Cys Asn  
 340 345 350  
 Leu Gly Ser Ile Asn Leu Ala Arg Met Leu Ala Asp Gly Arg Val Asp  
 355 360 365  
 Trp Asp Arg Leu Glu Glu Val Ala Gly Val Ala Val Arg Phe Leu Asp  
 370 375 380  
 Asp Val Ile Asp Val Ser Arg Tyr Pro Phe Pro Glu Leu Gly Glu Ala  
 385 390 395 400  
 Ala Arg Ala Thr Arg Lys Ile Gly Leu Gly Val Met Gly Leu Ala Glu  
 405 410 415  
 Leu Leu Ala Ala Leu Gly Ile Pro Tyr Asp Ser Glu Glu Ala Val Arg  
 420 425 430  
 Leu Ala Thr Arg Leu Met Arg Arg Ile Gln Gln Ala Ala His Thr Ala  
 435 440 445  
 Ser Arg Arg Leu Ala Glu Glu Arg Gly Ala Phe Pro Ala Phe Thr Asp  
 450 455 460

103

Ser Arg Phe Ala Arg Ser Gly Pro Arg Arg Asn Ala Gln Val Thr Ser  
 465 470 475 480

Val Ala Pro Thr Gly  
 485

## (2) INFORMATION FOR SEQ ID NO:71:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 267 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

Gly Val Ile Val Leu Asp Leu Glu Pro Arg Gly Pro Leu Pro Thr Glu  
 1 5 10 15

Ile Tyr Trp Arg Arg Arg Gly Leu Ala Leu Gly Ile Ala Val Val Val  
 20 25 30

Val Gly Ile Ala Val Ala Ile Val Ile Ala Phe Val Asp Ser Ser Ala  
 35 40 45

Gly Ala Lys Pro Val Ser Ala Asp Lys Pro Ala Ser Ala Gln Ser His  
 50 55 60

Pro Gly Ser Pro Ala Pro Gln Ala Pro Gln Pro Ala Gly Gln Thr Glu  
 65 70 75 80

Gly Asn Ala Ala Ala Ala Pro Pro Gln Gly Gln Asn Pro Glu Thr Pro  
 85 90 95

Thr Pro Thr Ala Ala Val Gln Pro Pro Pro Val Leu Lys Glu Gly Asp  
 100 105 110

Asp Cys Pro Asp Ser Thr Leu Ala Val Lys Gly Leu Thr Asn Ala Pro  
 115 120 125

Gln Tyr Tyr Val Gly Asp Gln Pro Lys Phe Thr Met Val Val Thr Asn

104

```

130
135
140
Ile Gly Leu Val Ser Cys Lys Arg Asp Val Gly Ala Ala Val Leu Ala
145      150      155      160
Ala Tyr Val Tyr Ser Leu Asp Asn Lys Arg Leu Trp Ser Asn Leu Asp
165      170      175
Cys Ala Pro Ser Asn Glu Thr Leu Val Lys Thr Phe Ser Pro Gly Glu
180      185      190
Gln Val Thr Thr Ala Val Thr Trp Thr Gly Met Gly Ser Ala Pro Arg
195      200      205
Cys Pro Leu Pro Arg Pro Ala Ile Gly Pro Gly Thr Tyr Asn Leu Val
210      215      220
Val Gln Leu Gly Asn Leu Arg Ser Leu Pro Val Pro Phe Ile Leu Asn
225      230      235      240
Gln Pro Pro Pro Pro Gly Pro Val Pro Ala Pro Gly Pro Ala Gln
245      250      255
Ala Pro Pro Pro Glu Ser Pro Ala Gln Gly Gly
260      265

```

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 97 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

Leu Ile Ser Thr Gly Lys Ala Ser His Ala Ser Leu Gly Val Gln Val  
1 5 10 15  
Thr Asn Asp Lys Asp Thr Pro Gly Ala Lys Ile Val Glu Val Val Ala  
20 25 30

Gly Gly Ala Ala Ala Asn Ala Gly Val Pro Lys Gly Val Val Val Thr  
35 40 45  
Lys Val<sup>+</sup> Asp Asp Arg Pro Ile Asn Ser Ala Asp Ala Leu Val Ala Ala  
50 55 60  
Val Arg Ser Lys Ala Pro Gly Ala Thr Val Ala Leu Thr Phe Gln Asp  
65 70 75 80  
Pro Ser Gly Gly Ser Arg Thr Val Gln Val Thr Leu Gly Lys Ala Glu  
85 90 95  
Gln

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 364 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

Gly Ala Ala Val Ser Leu Leu Ala Ala Gly Thr Leu Val Leu Thr Ala  
1 5 10 15

Cys Gly Gly Gly Thr Asn Ser Ser Ser Ser Gly Ala Gly Gly Thr Ser  
20 25 30

Gly Ser Val His Cys Gly Gly Lys Lys Glu Leu His Ser Ser Gly Ser  
35 40 45

Thr Ala Gln Glu Asn Ala Met Glu Gln Phe Val Tyr Ala Tyr Val Arg  
50 55 60

Ser Cys Pro Gly Tyr Thr Leu Asp Tyr Asn Ala Asn Gly Ser Gly Ala  
65 70 75 80

Gly Val Thr Gln Phe Leu Asn Asn Glu Thr Asp Phe Ala Gly Ser Asp  
85 90 95

Val Pro Leu Asn Pro Ser Thr Gly Gln Pro Asp Arg Ser Ala Glu Arg  
100 105 110

Cys Gly Ser Pro Ala Trp Asp Leu Pro Thr Val Phe Gly Pro Ile Ala  
115 120 125

Ile Thr Tyr Asn Ile Lys Gly Val Ser Thr Leu Asn Leu Asp Gly Pro  
130 135 140

Thr Thr Ala Lys Ile Phe Asn Gly Thr Ile Thr Val Trp Asn Asp Pro  
145 150 155 160

Gln Ile Gln Ala Leu Asn Ser Gly Thr Asp Leu Pro Pro Thr Pro Ile  
165 170 175

Ser Val Ile Phe Arg Ser Asp Lys Ser Gly Thr Ser Asp Asn Phe Gln  
180 185 190

Lys Tyr Leu Asp Gly Val Ser Asn Gly Ala Trp Gly Lys Gly Ala Ser  
195 200 205

Glu Thr Phe Ser Gly Gly Val Gly Val Gly Ala Ser Gly Asn Asn Gly  
210 215 220

Thr Ser Ala Leu Leu Gln Thr Thr Asp Gly Ser Ile Thr Tyr Asn Glu  
225 230 235 240

Trp Ser Phe Ala Val Gly Lys Gln Leu Asn Met Ala Gln Ile Ile Thr  
245 250 255

Ser Ala Gly Pro Asp Pro Val Ala Ile Thr Thr Glu Ser Val Gly Lys  
260 265 270

Thr Ile Ala Gly Ala Lys Ile Met Gly Gln Gly Asn Asp Leu Val Leu  
275 280 285

Asp Thr Ser Ser Phe Tyr Arg Pro Thr Gln Pro Gly Ser Tyr Pro Ile  
290 295 300

Val Leu Ala Thr Tyr Glu Ile Val Cys Ser Lys Tyr Pro Asp Ala Thr  
305 310 315 320

107

Thr Gly Thr Ala Val Arg Ala Phe Met Gln Ala Ala Ile Gly Pro Gly  
                                   325                                  330                                  335

Gln Glu Gly Leu Asp Gln Tyr Gly Ser Ile Pro Leu Pro Lys Ser Phe  
                                   340                                  345                                  350

Gln Ala Lys Leu Ala Ala Ala Val Asn Ala Ile Ser  
                                   355                                  360

## (2) INFORMATION FOR SEQ ID NO:74:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 309 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

Gln Ala Ala Ala Gly Arg Ala Val Arg Arg Thr Gly His Ala Glu Asp  
   1                                  5                                  10                                  15

Gln Thr His Gln Asp Arg Leu His His Gly Cys Arg Arg Ala Ala Val  
                                   20                                  25                                  30

Val Val Arg Gln Asp Arg Ala Ser Val Ser Ala Thr Ser Ala Arg Pro  
                                   35                                  40                                  45

Pro Arg Arg His Pro Ala Gln Gly His Arg Arg Arg Val Ala Pro Ser  
                                   50                                  55                                  60

Gly Gly Arg Arg Arg Pro His Pro His His Val Gln Pro Asp Asp Arg  
   65                                  70                                  75                                  80

Arg Asp Arg Pro Ala Leu Leu Asp Arg Thr Gln Pro Ala Glu His Pro  
                                   85                                  90                                  95

Asp Pro His Arg Arg Gly Pro Ala Asp Pro Gly Arg Val Arg Gly Arg  
                                   100                                  105                                  110

Gly Arg Leu Arg Arg Val Asp Asp Gly Arg Leu Gln Pro Asp Arg Asp

108

115	120	125
Ala Asp His Gly Ala Pro Val Arg Gly Arg Gly Pro His Arg Gly Val		
130	135	140
Gln His Arg Gly Gly Pro Val Phe Val Arg Arg Val Pro Gly Val Arg		
145	150	155
		160
Cys Ala His Arg Arg Gly His Arg Arg Val Ala Ala Pro Gly Gln Gly		
165	170	175
Asp Val Leu Arg Ala Gly Leu Arg Val Glu Arg Leu Arg Pro Val Ala		
180	185	190
Ala Val Glu Asn Leu His Arg Gly Ser Gln Arg Ala Asp Gly Arg Val		
195	200	205
Phe Arg Pro Ile Arg Arg Gly Ala Arg Leu Pro Ala Arg Arg Ser Arg		
210	215	220
Ala Gly Pro Gln Gly Arg Leu His Leu Asp Gly Ala Gly Pro Ser Pro		
225	230	235
		240
Leu Pro Ala Arg Ala Gly Gln Gln Gln Pro Ser Ser Ala Gly Gly Arg		
245	250	255
Arg Ala Gly Gly Ala Glu Arg Ala Asp Pro Gly Gln Arg Gly Arg His		
260	265	270
His Gln Gly Gly His Asp Pro Gly Arg Gln Gly Ala Gln Arg Gly Thr		
275	280	285
Ala Gly Val Ala His Ala Ala Ala Gly Pro Arg Arg Ala Ala Val Arg		
290	295	300
Asn Arg Pro Arg Arg		
305		

## (2) INFORMATION FOR SEQ ID NO:75:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 580 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

Ser	Ala	Val	Trp	Cys	Leu	Asn	Gly	Phe	Thr	Gly	Arg	His	Arg	His	Gly	1	5	10	15
Arg	Cys	Arg	Val	Arg	Ala	Ser	Gly	Trp	Arg	Ser	Ser	Asn	Arg	Trp	Cys	20	25	30	
Ser	Thr	Thr	Ala	Asp	Cys	Cys	Ala	Ser	Lys	Thr	Pro	Thr	Gln	Ala	Ala	35	40	45	
Ser	Pro	Leu	Glu	Arg	Arg	Phe	Thr	Cys	Cys	Ser	Pro	Ala	Val	Gly	Cys	50	55	60	
Arg	Phe	Arg	Ser	Phe	Pro	Val	Arg	Arg	Leu	Ala	Leu	Gly	Ala	Arg	Thr	65	70	75	80
Ser	Arg	Thr	Leu	Gly	Val	Arg	Arg	Thr	Leu	Ser	Gln	Trp	Asn	Leu	Ser	85	90	95	
Pro	Arg	Ala	Gln	Pro	Ser	Cys	Ala	Val	Thr	Val	Glu	Ser	His	Thr	His	100	105	110	
Ala	Ser	Pro	Arg	Met	Ala	Lys	Leu	Ala	Arg	Val	Val	Gly	Leu	Val	Gln	115	120	125	
Glu	Glu	Gln	Pro	Ser	Asp	Met	Thr	Asn	His	Pro	Arg	Tyr	Ser	Pro	Pro	130	135	140	
Pro	Gln	Gln	Pro	Gly	Thr	Pro	Gly	Tyr	Ala	Gln	Gly	Gln	Gln	Gln	Thr	145	150	155	160
Tyr	Ser	Gln	Gln	Phe	Asp	Trp	Arg	Tyr	Pro	Pro	Ser	Pro	Pro	Pro	Gln	165	170	175	
Pro	Thr	Gln	Tyr	Arg	Gln	Pro	Tyr	Glu	Ala	Leu	Gly	Gly	Thr	Arg	Pro	180	185	190	
Gly	Leu	Ile	Pro	Gly	Val	Ile	Pro	Thr	Met	Thr	Pro	Pro	Pro	Gly	Met	195	200	205	

110

Val Arg Gln Arg Pro Arg Ala Gly Met Leu Ala Ile Gly Ala Val Thr  
 210 215 220  
 Ile Ala Val Val Ser Ala Gly Ile Gly Gly Ala Ala Ala Ser Leu Val  
 225 230 235 240  
 Gly Phe Asn Arg Ala Pro Ala Gly Pro Ser Gly Gly Pro Val Ala Ala  
 245 250 255  
 Ser Ala Ala Pro Ser Ile Pro Ala Ala Asn Met Pro Pro Gly Ser Val  
 260 265 270  
 Glu Gln Val Ala Ala Lys Val Val Pro Ser Val Val Met Leu Glu Thr  
 275 280 285  
 Asp Leu Gly Arg Gln Ser Glu Glu Gly Ser Gly Ile Ile Leu Ser Ala  
 290 295 300  
 Glu Gly Leu Ile Leu Thr Asn Asn His Val Ile Ala Ala Ala Ala Lys  
 305 310 315 320  
 Pro Pro Leu Gly Ser Pro Pro Pro Lys Thr Thr Val Thr Phe Ser Asp  
 325 330 335  
 Gly Arg Thr Ala Pro Phe Thr Val Val Gly Ala Asp Pro Thr Ser Asp  
 340 345 350  
 Ile Ala Val Val Arg Val Gln Gly Val Ser Gly Leu Thr Pro Ile Ser  
 355 360 365  
 Leu Gly Ser Ser Ser Asp Leu Arg Val Gly Gln Pro Val Leu Ala Ile  
 370 375 380  
 Gly Ser Pro Leu Gly Leu Glu Gly Thr Val Thr Thr Gly Ile Val Ser  
 385 390 395 400  
 Ala Leu Asn Arg Pro Val Ser Thr Thr Gly Glu Ala Gly Asn Gln Asn  
 405 410 415  
 Thr Val Leu Asp Ala Ile Gln Thr Asp Ala Ala Ile Asn Pro Gly Asn  
 420 425 430  
 Ser Gly Gly Ala Leu Val Asn Met Asn Ala Gln Leu Val Gly Val Asn  
 435 440 445

111

Ser Ala Ile Ala Thr Leu Gly Ala Asp Ser Ala Asp Ala Gln Ser Gly  
 450 455 460  
 Ser Ile Gly Leu Gly Phe Ala Ile Pro Val Asp Gln Ala Lys Arg Ile  
 465 470 475 480  
 Ala Asp Glu Leu Ile Ser Thr Gly Lys Ala Ser His Ala Ser Leu Gly  
 485 490 495  
 Val Gln Val Thr Asn Asp Lys Asp Thr Pro Gly Ala Lys Ile Val Glu  
 500 505 510  
 Val Val Ala Gly Gly Ala Ala Ala Asn Ala Gly Val Pro Lys Gly Val  
 515 520 525  
 Val Val Thr Lys Val Asp Asp Arg Pro Ile Asn Ser Ala Asp Ala Leu  
 530 535 540  
 Val Ala Ala Val Arg Ser Lys Ala Pro Gly Ala Thr Val Ala Leu Thr  
 545 550 555 560  
 Phe Gln Asp Pro Ser Gly Gly Ser Arg Thr Val Gln Val Thr Leu Gly  
 565 570 575  
 Lys Ala Glu Gln  
 580

## (2) INFORMATION FOR SEQ ID NO:76:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 233 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

Met Asn Asp Gly Lys Arg Ala Val Thr Ser Ala Val Leu Val Val Leu  
 1 5 10 15

112

Gly Ala Cys Leu Ala Leu Trp Leu Ser Gly Cys Ser Ser Pro Lys Pro  
                   20                  25                  30  
 Asp Ala Glu Glu Gln Gly Val Pro Val Ser Pro Thr Ala Ser Asp Pro  
           35                  40                  45  
 Ala Leu Leu Ala Glu Ile Arg Gln Ser Leu Asp Ala Thr Lys Gly Leu  
       50                  55                  60  
 Thr Ser Val His Val Ala Val Arg Thr Thr Gly Lys Val Asp Ser Leu  
   65                  70                  75                  80  
 Leu Gly Ile Thr Ser Ala Asp Val Asp Val Arg Ala Asn Pro Leu Ala  
                   85                  90                  95  
 Ala Lys Gly Val Cys Thr Tyr Asn Asp Glu Gln Gly Val Pro Phe Arg  
                   100                  105                  110  
 Val Gln Gly Asp Asn Ile Ser Val Lys Leu Phe Asp Asp Trp Ser Asn  
           115                  120                  125  
 Leu Gly Ser Ile Ser Glu Leu Ser Thr Ser Arg Val Leu Asp Pro Ala  
       130                  135                  140  
 Ala Gly Val Thr Gln Leu Leu Ser Gly Val Thr Asn Leu Gln Ala Gln  
   145                  150                  155                  160  
 Gly Thr Glu Val Ile Asp Gly Ile Ser Thr Thr Lys Ile Thr Gly Thr  
                   165                  170                  175  
 Ile Pro Ala Ser Ser Val Lys Met Leu Asp Pro Gly Ala Lys Ser Ala  
           180                  185                  190  
 Arg Pro Ala Thr Val Trp Ile Ala Gln Asp Gly Ser His His Leu Val  
       195                  200                  205  
 Arg Ala Ser Ile Asp Leu Gly Ser Gly Ser Ile Gln Leu Thr Gln Ser  
       210                  215                  220  
 Lys Trp Asn Glu Pro Val Asn Val Asp  
   225                  230

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:

113

- (A) LENGTH: 66 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

```

Val Ile Asp Ile Ile Gly Thr Ser Pro Thr Ser Trp Glu Gln Ala Ala
1           5           10           15
Ala Glu Ala Val Gln Arg Ala Arg Asp Ser Val Asp Asp Ile Arg Val
          20           25           30
Ala Arg Val Ile Glu Gln Asp Met Ala Val Asp Ser Ala Gly Lys Ile
          35           40           45
Thr Tyr Arg Ile Lys Leu Glu Val Ser Phe Lys Met Arg Pro Ala Gln
          50           55           60
Pro Arg
          65

```

(2) INFORMATION FOR SEQ ID NO:78:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 69 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

```

Val Pro Pro Ala Pro Pro Leu Pro Pro Leu Pro Pro Ser Pro Ile Ser
1           5           10           15
Cys Ala Ser Pro Pro Ser Pro Pro Leu Pro Pro Ala Pro Pro Val Ala
          20           25           30

```

Pro Gly Pro Pro Met Pro Pro Leu Asp Pro Trp Pro Pro Ala Pro Pro  
35 40 45

Leu Pro Tyr Ser Thr Pro Pro Gly Ala Pro Leu Pro Pro Ser Pro Pro  
50 55 60

Ser Pro Pro Leu Pro  
65

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 355 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

Met Ser Asn Ser Arg Arg Arg Ser Leu Arg Trp Ser Trp Leu Leu Ser  
1 5 10 15

Val Leu Ala Ala Val Gly Leu Gly Leu Ala Thr Ala Pro Ala Gln Ala  
20 25 30

Ala Pro Pro Ala Leu Ser Gln Asp Arg Phe Ala Asp Phe Pro Ala Leu  
35 40 45

Pro Leu Asp Pro Ser Ala Met Val Ala Gln Val Ala Pro Gln Val Val  
50 55 60

Asn Ile Asn Thr Lys Leu Gly Tyr Asn Asn Ala Val Gly Ala Gly Thr  
65 70 75 80

Gly Ile Val Ile Asp Pro Asn Gly Val Val Leu Thr Asn Asn His Val  
85 90 95

Ile Ala Gly Ala Thr Asp Ile Asn Ala Phe Ser Val Gly Ser Gly Gln  
100 105 110

115

Thr Tyr Gly Val Asp Val Val Gly Tyr Asp Arg Thr Gln Asp Val Ala  
 115 120 125  
 Val Leu Gln Leu Arg Gly Ala Gly Gly Leu Pro Ser Ala Ala Ile Gly  
 130 135 140  
 Gly Gly Val Ala Val Gly Glu Pro Val Val Ala Met Gly Asn Ser Gly  
 145 150 155 160  
 Gly Gln Gly Gly Thr Pro Arg Ala Val Pro Gly Arg Val Val Ala Leu  
 165 170 175  
 Gly Gln Thr Val Gln Ala Ser Asp Ser Leu Thr Gly Ala Glu Glu Thr  
 180 185 190  
 Leu Asn Gly Leu Ile Gln Phe Asp Ala Ala Ile Gln Pro Gly Asp Ser  
 195 200 205  
 Gly Gly Pro Val Val Asn Gly Leu Gly Gln Val Val Gly Met Asn Thr  
 210 215 220  
 Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe Ala  
 225 230 235 240  
 Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser Gly  
 245 250 255  
 Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly Leu  
 260 265 270  
 Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val Val  
 275 280 285  
 Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val Ile  
 290 295 300  
 Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala Asp  
 305 310 315 320  
 Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp Gln  
 325 330 335  
 Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu Gly  
 340 345 350

Pro Pro Ala  
355

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 205 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

Ser	Pro	Lys	Pro	Asp	Ala	Glu	Glu	Gln	Gly	Val	Pro	Val	Ser	Pro	Thr	1	5	10	15
Ala	Ser	Asp	Pro	Ala	Leu	Leu	Ala	Glu	Ile	Arg	Gln	Ser	Leu	Asp	Ala	20	25	30	
Thr	Lys	Gly	Leu	Thr	Ser	Val	His	Val	Ala	Val	Arg	Thr	Thr	Gly	Lys	35	40	45	
Val	Asp	Ser	Leu	Leu	Gly	Ile	Thr	Ser	Ala	Asp	Val	Asp	Val	Arg	Ala	50	55	60	
Asn	Pro	Leu	Ala	Ala	Lys	Gly	Val	Cys	Thr	Tyr	Asn	Asp	Glu	Gln	Gly	65	70	75	80
Val	Pro	Phe	Arg	Val	Gln	Gly	Asp	Asn	Ile	Ser	Val	Lys	Leu	Phe	Asp	85	90	95	
Asp	Trp	Ser	Asn	Leu	Gly	Ser	Ile	Ser	Glu	Leu	Ser	Thr	Ser	Arg	Val	100	105	110	
Leu	Asp	Pro	Ala	Ala	Gly	Val	Thr	Gln	Leu	Leu	Ser	Gly	Val	Thr	Asn	115	120	125	
Leu	Gln	Ala	Gln	Gly	Thr	Glu	Val	Ile	Asp	Gly	Ile	Ser	Thr	Thr	Lys	130	135	140	
Ile	Thr	Gly	Thr	Ile	Pro	Ala	Ser	Ser	Val	Lys	Met	Leu	Asp	Pro	Gly				

117

145                      150                      155                      160  
 Ala Lys Ser Ala Arg Pro Ala Thr Val Trp Ile Ala Gln Asp Gly Ser  
                                  165                      170                      175  
 His His Leu Val Arg Ala Ser Ile Asp Leu Gly Ser Gly Ser Ile Gln  
                                  180                      185                      190  
 Leu Thr Gln Ser Lys Trp Asn Glu Pro Val Asn Val Asp  
                                  195                      200                      205

## (2) INFORMATION FOR SEQ ID NO:81:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 286 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

Gly Asp Ser Phe Trp Ala Ala Ala Asp Gln Met Ala Arg Gly Phe Val  
 1                      5                      10                      15  
 Leu Gly Ala Thr Ala Gly Arg Thr Thr Leu Thr Gly Glu Gly Leu Gln  
                                  20                      25                      30  
 His Ala Asp Gly His Ser Leu Leu Leu Asp Ala Thr Asn Pro Ala Val  
                                  35                      40                      45  
 Val Ala Tyr Asp Pro Ala Phe Ala Tyr Glu Ile Gly Tyr Ile Xaa Glu  
                                  50                      55                      60  
 Ser Gly Leu Ala Arg Met Cys Gly Glu Asn Pro Glu Asn Ile Phe Phe  
 65                      70                      75                      80  
 Tyr Ile Thr Val Tyr Asn Glu Pro Tyr Val Gln Pro Pro Glu Pro Glu  
                                  85                      90                      95  
 Asn Phe Asp Pro Glu Gly Val Leu Gly Gly Ile Tyr Arg Tyr His Ala  
                                  100                      105                      110

118

Ala Thr Glu Gln Arg Thr Asn Lys Xaa Gln Ile Leu Ala Ser Gly Val  
 115 120 125  
 Ala Met Pro Ala Ala Leu Arg Ala Ala Gln Met Leu Ala Ala Glu Trp  
 130 135 140  
 Asp Val Ala Ala Asp Val Trp Ser Val Thr Ser Trp Gly Glu Leu Asn  
 145 150 155 160  
 Arg Asp Gly Val Val Ile Glu Thr Glu Lys Leu Arg His Pro Asp Arg  
 165 170 175  
 Pro Ala Gly Val Pro Tyr Val Thr Arg Ala Leu Glu Asn Ala Arg Gly  
 180 185 190  
 Pro Val Ile Ala Val Ser Asp Trp Met Arg Ala Val Pro Glu Gln Ile  
 195 200 205  
 Arg Pro Trp Val Pro Gly Thr Tyr Leu Thr Leu Gly Thr Asp Gly Phe  
 210 215 220  
 Gly Phe Ser Asp Thr Arg Pro Ala Gly Arg Arg Tyr Phe Asn Thr Asp  
 225 230 235 240  
 Ala Glu Ser Gln Val Gly Arg Gly Phe Gly Arg Gly Trp Pro Gly Arg  
 245 250 255  
 Arg Val Asn Ile Asp Pro Phe Gly Ala Gly Arg Gly Pro Pro Ala Gln  
 260 265 270  
 Leu Pro Gly Phe Asp Glu Gly Gly Gly Leu Arg Pro Xaa Lys  
 275 280 285

## (2) INFORMATION FOR SEQ ID NO:82:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 173 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear



120

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

Arg Ala Asp Glu Arg Lys Asn Thr Thr Met Lys Met Val Lys Ser Ile  
 1                      5                      10                      15  
 Ala Ala Gly Leu Thr Ala Ala Ala Ala Ile Gly Ala Ala Ala Ala Gly  
                     20                      25                      30  
 Val Thr Ser Ile Met Ala Gly Gly Pro Val Val Tyr Gln Met Gln Pro  
                     35                      40                      45  
 Val Val Phe Gly Ala Pro Leu Pro Leu Asp Pro Xaa Ser Ala Pro Xaa  
                     50                      55                      60  
 Val Pro Thr Ala Ala Gln Trp Thr Xaa Leu Leu Asn Xaa Leu Xaa Asp  
 65                      70                      75                      80  
 Pro Asn Val Ser Phe Xaa Asn Lys Gly Ser Leu Val Glu Gly Gly Ile  
                     85                      90                      95  
 Gly Gly Xaa Glu Gly Xaa Xaa Arg Arg Xaa Gln  
                     100                      105

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 125 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

Val Leu Ser Val Pro Val Gly Asp Gly Phe Trp Xaa Arg Val Val Asn  
 1                      5                      10                      15  
 Pro Leu Gly Gln Pro Ile Asp Gly Arg Gly Asp Val Asp Ser Asp Thr  
                     20                      25                      30

121

Arg Arg Ala Leu Glu Leu Gln Ala Pro Ser Val Val Xaa Arg Gln Gly  
           35                          40                          45  
 Val Lys Glu Pro Leu Xaa Thr Gly Ile Lys Ala Ile Asp Ala Met Thr  
       50                          55                          60  
 Pro Ile Gly Arg Gly Gln Arg Gln Leu Ile Ile Gly Asp Arg Lys Thr  
   65                          70                          75                          80  
 Gly Lys Asn Arg Arg Leu Cys Arg Thr Pro Ser Ser Asn Gln Arg Glu  
                           85                          90                          95  
 Glu Leu Gly Val Arg Trp Ile Pro Arg Ser Arg Cys Ala Cys Val Tyr  
           100                          105                          110  
 Val Gly His Arg Ala Arg Arg Gly Thr Tyr His Arg Arg  
       115                          120                          125

## (2) INFORMATION FOR SEQ ID NO:85:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 117 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

Cys Asp Ala Val Met Gly Phe Leu Gly Gly Ala Gly Pro Leu Ala Val  
 1                          5                          10                          15  
 Val Asp Gln Gln Leu Val Thr Arg Val Pro Gln Gly Trp Ser Phe Ala  
           20                          25                          30  
 Gln Ala Ala Ala Val Pro Val Val Phe Leu Thr Ala Trp Tyr Gly Leu  
       35                          40                          45  
 Ala Asp Leu Ala Glu Ile Lys Ala Gly Glu Ser Val Leu Ile His Ala  
       50                          55                          60  
 Gly Thr Gly Gly Val Gly Met Ala Ala Val Gln Leu Ala Arg Gln Trp

65                      70                      75                      80

Gly Val Glu Val Phe Val Thr Ala Ser Arg Gly Lys Trp Asp Thr Leu  
                      85                      90                      95

Arg Ala Xaa Xaa Phe Asp Asp Xaa Pro Tyr Arg Xaa Phe Pro His Xaa  
                      100                      105                      110

Arg Ser Ser Xaa Gly  
                      115

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 103 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

Met Tyr Arg Phe Ala Cys Arg Thr Leu Met Leu Ala Ala Cys Ile Leu  
1 5 10 15  
Ala Thr Gly Val Ala Gly Leu Gly Val Gly Ala Gln Ser Ala Ala Gln  
20 25 30  
Thr Ala Pro Val Pro Asp Tyr Tyr Trp Cys Pro Gly Gln Pro Phe Asp  
35 40 45  
Pro Ala Trp Gly Pro Asn Trp Asp Pro Tyr Thr Cys His Asp Asp Phe  
50 55 60  
His Arg Asp Ser Asp Gly Pro Asp His Ser Arg Asp Tyr Pro Gly Pro  
65 70 75 80  
Ile Leu Glu Gly Pro Val Leu Asp Asp Pro Gly Ala Ala Pro Pro Pro  
85 90 95  
Pro Ala Ala Gly Gly Gly Ala  
100

## (2) INFORMATION FOR SEQ ID NO:87:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 88 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

```

Val Gln Cys Arg Val Trp Leu Glu Ile Gln Trp Arg Gly Met Leu Gly
 1             5             10             15
Ala Asp Gln Ala Arg Ala Gly Gly Pro Ala Arg Ile Trp Arg Glu His
          20             25             30
Ser Met Ala Ala Met Lys Pro Arg Thr Gly Asp Gly Pro Leu Glu Ala
          35             40             45
Thr Lys Glu Gly Arg Gly Ile Val Met Arg Val Pro Leu Glu Gly Gly
 50             55             60
Gly Arg Leu Val Val Glu Leu Thr Pro Asp Glu Ala Ala Ala Leu Gly
65             70             75             80
Asp Glu Leu Lys Gly Val Thr Ser
          85

```

## (2) INFORMATION FOR SEQ ID NO:88:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 95 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

124

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

Thr Asp Ala Ala Thr Leu Ala Gln Glu Ala Gly Asn Phe Glu Arg Ile  
 1                      5                      10                      15  
 Ser Gly Asp Leu Lys Thr Gln Ile Asp Gln Val Glu Ser Thr Ala Gly  
                     20                      25                      30  
 Ser Leu Gln Gly Gln Trp Arg Gly Ala Ala Gly Thr Ala Ala Gln Ala  
                     35                      40                      45  
 Ala Val Val Arg Phe Gln Glu Ala Ala Asn Lys Gln Lys Gln Glu Leu  
                     50                      55                      60  
 Asp Glu Ile Ser Thr Asn Ile Arg Gln Ala Gly Val Gln Tyr Ser Arg  
 65                      70                      75                      80  
 Ala Asp Glu Glu Gln Gln Gln Ala Leu Ser Ser Gln Met Gly Phe  
                     85                      90                      95

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 166 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

Met Thr Gln Ser Gln Thr Val Thr Val Asp Gln Gln Glu Ile Leu Asn  
 1                      5                      10                      15  
 Arg Ala Asn Glu Val Glu Ala Pro Met Ala Asp Pro Pro Thr Asp Val  
                     20                      25                      30  
 Pro Ile Thr Pro Cys Glu Leu Thr Xaa Xaa Lys Asn Ala Ala Gln Gln  
                     35                      40                      45  
 Xaa Val Leu Ser Ala Asp Asn Met Arg Glu Tyr Leu Ala Ala Gly Ala  
                     50                      55                      60

125

Lys Glu Arg Gln Arg Leu Ala Thr Ser Leu Arg Asn Ala Ala Lys Xaa  
 65 70 75 80

Tyr Gly Glu Val Asp Glu Glu Ala Ala Thr Ala Leu Asp Asn Asp Gly  
 85 90 95

Glu Gly Thr Val Gln Ala Glu Ser Ala Gly Ala Val Gly Gly Asp Ser  
 100 105 110

Ser Ala Glu Leu Thr Asp Thr Pro Arg Val Ala Thr Ala Gly Glu Pro  
 115 120 125

Asn Phe Met Asp Leu Lys Glu Ala Ala Arg Lys Leu Glu Thr Gly Asp  
 130 135 140

Gln Gly Ala Ser Leu Ala His Xaa Gly Asp Gly Trp Asn Thr Xaa Thr  
 145 150 155 160

Leu Thr Leu Gln Gly Asp  
 165

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 5 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

Arg Ala Glu Arg Met  
 1 5

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 263 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single

126

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

Val Ala Trp Met Ser Val Thr Ala Gly Gln Ala Glu Leu Thr Ala Ala  
 1 5 10 15  
 Gln Val Arg Val Ala Ala Ala Tyr Glu Thr Ala Tyr Gly Leu Thr  
 20 25 30  
 Val Pro Pro Pro Val Ile Ala Glu Asn Arg Ala Glu Leu Met Ile Leu  
 35 40 45  
 Ile Ala Thr Asn Leu Leu Gly Gln Asn Thr Pro Ala Ile Ala Val Asn  
 50 55 60  
 Glu Ala Glu Tyr Gly Glu Met Trp Ala Gln Asp Ala Ala Ala Met Phe  
 65 70 75 80  
 Gly Tyr Ala Ala Ala Thr Ala Thr Ala Thr Ala Thr Leu Leu Pro Phe  
 85 90 95  
 Glu Glu Ala Pro Glu Met Thr Ser Ala Gly Gly Leu Leu Glu Gln Ala  
 100 105 110  
 Ala Ala Val Glu Glu Ala Ser Asp Thr Ala Ala Ala Asn Gln Leu Met  
 115 120 125  
 Asn Asn Val Pro Gln Ala Leu Lys Gln Leu Ala Gln Pro Thr Gln Gly  
 130 135 140  
 Thr Thr Pro Ser Ser Lys Leu Gly Gly Leu Trp Lys Thr Val Ser Pro  
 145 150 155 160  
 His Arg Ser Pro Ile Ser Asn Met Val Ser Met Ala Asn Asn His Met  
 165 170 175  
 Ser Met Thr Asn Ser Gly Val Ser Met Thr Asn Thr Leu Ser Ser Met  
 180 185 190  
 Leu Lys Gly Phe Ala Pro Ala Ala Ala Ala Gln Ala Val Gln Thr Ala

127

195	200	205
Ala Gln Asn Gly Val Arg Ala Met Ser Ser Leu Gly Ser Ser Leu Gly		
210	215	220
Ser Ser Gly Leu Gly Gly Gly Val Ala Ala Asn Leu Gly Arg Ala Ala		
225	230	235 240
Ser Val Arg Tyr Gly His Arg Asp Gly Gly Lys Tyr Ala Xaa Ser Gly		
245	250	255
Arg Arg Asn Gly Gly Pro Ala		
260		

## (2) INFORMATION FOR SEQ ID NO:92:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 303 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

Met Thr Tyr Ser Pro Gly Asn Pro Gly Tyr Pro Gln Ala Gln Pro Ala		
1	5	10 15
Gly Ser Tyr Gly Gly Val Thr Pro Ser Phe Ala His Ala Asp Glu Gly		
20	25	30
Ala Ser Lys Leu Pro Met Tyr Leu Asn Ile Ala Val Ala Val Leu Gly		
35	40	45
Leu Ala Ala Tyr Phe Ala Ser Phe Gly Pro Met Phe Thr Leu Ser Thr		
50	55	60
Glu Leu Gly Gly Gly Asp Gly Ala Val Ser Gly Asp Thr Gly Leu Pro		
65	70	75 80
Val Gly Val Ala Leu Leu Ala Ala Leu Leu Ala Gly Val Val Leu Val		
85	90	95

128

Pro Lys Ala Lys Ser His Val Thr Val Val Ala Val Leu Gly Val Leu  
                   100                                  105                                  110

Gly Val Phe Leu Met Val Ser Ala Thr Phe Asn Lys Pro Ser Ala Tyr  
                   115                                  120                                  125

Ser Thr Gly Trp Ala Leu Trp Val Val Leu Ala Phe Ile Val Phe Gln  
                   130                                  135                                  140

Ala Val Ala Ala Val Leu Ala Leu Leu Val Glu Thr Gly Ala Ile Thr  
                   145                                  150                                  155                                  160

Ala Pro Ala Pro Arg Pro Lys Phe Asp Pro Tyr Gly Gln Tyr Gly Arg  
                                   165                                  170                                  175

Tyr Gly Gln Tyr Gly Gln Tyr Gly Val Gln Pro Gly Gly Tyr Tyr Gly  
                   180                                  185                                  190

Gln Gln Gly Ala Gln Gln Ala Ala Gly Leu Gln Ser Pro Gly Pro Gln  
                   195                                  200                                  205

Gln Ser Pro Gln Pro Pro Gly Tyr Gly Ser Gln Tyr Gly Gly Tyr Ser  
                   210                                  215                                  220

Ser Ser Pro Ser Gln Ser Gly Ser Gly Tyr Thr Ala Gln Pro Pro Ala  
                   225                                  230                                  235                                  240

Gln Pro Pro Ala Gln Ser Gly Ser Gln Gln Ser His Gln Gly Pro Ser  
                                   245                                  250                                  255

Thr Pro Pro Thr Gly Phe Pro Ser Phe Ser Pro Pro Pro Pro Val Ser  
                   260                                  265                                  270

Ala Gly Thr Gly Ser Gln Ala Gly Ser Ala Pro Val Asn Tyr Ser Asn  
                   275                                  280                                  285

Pro Ser Gly Gly Glu Gln Ser Ser Ser Pro Gly Gly Ala Pro Val  
                   290                                  295                                  300

## (2) INFORMATION FOR SEQ ID NO:93:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28 amino acids

(B) TYPE: amino acid

129

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

Gly Cys Gly Glu Thr Asp Ala Ala Thr Leu Ala Gln Glu Ala Gly Asn  
1                      5                      10                      15

Phe Glu Arg Ile Ser Gly Asp Leu Lys Thr Gln Ile  
                    20                      25

(2) INFORMATION FOR SEQ ID NO:94:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 16 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

Asp Gln Val Glu Ser Thr Ala Gly Ser Leu Gln Gly Gln Trp Arg Gly  
1                      5                      10                      15

(2) INFORMATION FOR SEQ ID NO:95:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 27 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

130

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

Gly Cys Gly Ser Thr Ala Gly Ser Leu Gln Gly Gln Trp Arg Gly Ala  
 1 5 10 15

Ala Gly Thr Ala Ala Gln Ala Ala Val Val Arg  
 20 25

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

Gly Cys Gly Gly Thr Ala Ala Gln Ala Ala Val Val Arg Phe Gln Glu  
 1 5 10 15

Ala Ala Asn Lys Gln Lys Gln Glu Leu Asp Glu  
 20 25

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

Gly Cys Gly Ala Asn Lys Gln Lys Gln Glu Leu Asp Glu Ile Ser Thr  
 1 5 10 15

131

Asn Ile Arg Gln Ala Gly Val Gln Tyr Ser Arg  
                   20                                  25

## (2) INFORMATION FOR SEQ ID NO:98:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 28 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

Gly Cys Gly Ile Arg Gln Ala Gly Val Gln Tyr Ser Arg Ala Asp Glu  
   1                                  5                                  10                                  15

Glu Gln Gln Gln Ala Leu Ser Ser Gln Met Gly Phe  
                                   20                                  25

## (2) INFORMATION FOR SEQ ID NO:99:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 507 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

ATGAAGATGG TGAAATCGAT CGCCGCAGGT CTGACCGCCG CGGCTGCAAT CGGCGCCGCT	60
GCGGCCGGTG TGAATTCGAT CATGGCTGGC GGCCCGGTCTG TATACCAGAT GCAGCCGGTC	120
GTCTTCGGCG CGCCACTGCC GTTGGACCCG GCATCCGCCC CTGACGTCCC GACCGCCGCC	180
CAGTTGACCA GCCTGCTCAA CAGCCTCGCC GATCCCAACG TGTCGTTTGC GAACAAGGGC	240

AGTCTGGTCG AGGGCGGCAT CGGGGGCACC GAGGCGCGCA TCGCCGACCA CAAGCTGAAG 300  
 AAGGCCGCCG AGCACGGGGA TCTGCCGCTG TCGTTCAGCG TGACGAACAT CCAGCCGGCG 360  
 GCCGCCGGTT CGGCCACCGC CGACGTTTCC GTCTCGGGTC CGAAGCTCTC GTCGCCGGTC 420  
 ACGCAGAACG TCACGTTTCGT GAATCAAGGC GGCTGGATGC TGTCACGCGC ATCGGCGATG 480  
 GAGTTGCTGC AGGCCGCAGG GAACTGA 507

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 168 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

Met Lys Met Val Lys Ser Ile Ala Ala Gly Leu Thr Ala Ala Ala Ala  
 1 5 10 15  
 Ile Gly Ala Ala Ala Ala Gly Val Thr Ser Ile Met Ala Gly Gly Pro  
 20 25 30  
 Val Val Tyr Gln Met Gln Pro Val Val Phe Gly Ala Pro Leu Pro Leu  
 35 40 45  
 Asp Pro Ala Ser Ala Pro Asp Val Pro Thr Ala Ala Gln Leu Thr Ser  
 50 55 60  
 Leu Leu Asn Ser Leu Ala Asp Pro Asn Val Ser Phe Ala Asn Lys Gly  
 65 70 75 80  
 Ser Leu Val Glu Gly Gly Ile Gly Gly Thr Glu Ala Arg Ile Ala Asp  
 85 90 95  
 His Lys Leu Lys Lys Ala Ala Glu His Gly Asp Leu Pro Leu Ser Phe  
 100 105 110

133

Ser Val Thr Asn Ile Gln Pro Ala Ala Ala Gly Ser Ala Thr Ala Asp  
 115 120 125

Val Ser Val Ser Gly Pro Lys Leu Ser Ser Pro Val Thr Gln Asn Val  
 130 135 140

Thr Phe Val Asn Gln Gly Gly Trp Met Leu Ser Arg Ala Ser Ala Met  
 145 150 155 160

Glu Leu Leu Gln Ala Ala Gly Asn  
 165

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 500 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

CGTGGCAATG TCGTTGACCG TCGGGGCCGG GGTGCCTCC GCAGATCCCG TGGACGCGGT	60
CATTAACACC ACCTGCAATT ACGGGCAGGT AGTAGCTGCG CTCAACGCGA CGGATCCGGG	120
GGCTGCCGCA CAGTTCAACG CCTCACCAGT GGCGCAGTCC TATTTGCGCA ATTCCTCGC	180
CGCACCGCCA CCTCAGCGCG CTGCCATGGC CGCGCAATTG CAAGCTGTGC CGGGGGCGGC	240
ACAGTACATC GGCCTTGTCG AGTCGGTTGC CGGCTCCTGC AACAACTATT AAGCCCATGC	300
GGGCCCCATC CCGCGACCCG GCATCGTCGC CGGGGCTAGG CCAGATTGCC CCGCTCCTCA	360
ACGGGCGGCA TCCGCGACC CGGCATCGTC GCCGGGGCTA GGCCAGATTG CCCCCTCCT	420
CAACGGGCCG CATCTCGTGC CGAATTCCTG CAGCCCGGGG GATCCACTAG TTCTAGAGCG	480
GCCGCCACCG CGGTGGAGCT	500

## (2) INFORMATION FOR SEQ ID NO:102:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 96 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

```

Val Ala Met Ser Leu Thr Val Gly Ala Gly Val Ala Ser Ala Asp Pro
1           5           10           15
Val Asp Ala Val Ile Asn Thr Thr Cys Asn Tyr Gly Gln Val Val Ala
20           25           30
Ala Leu Asn Ala Thr Asp Pro Gly Ala Ala Ala Gln Phe Asn Ala Ser
35           40           45
Pro Val Ala Gln Ser Tyr Leu Arg Asn Phe Leu Ala Ala Pro Pro Pro
50           55           60
Gln Arg Ala Ala Met Ala Ala Gln Leu Gln Ala Val Pro Gly Ala Ala
65           70           75           80
Gln Tyr Ile Gly Leu Val Glu Ser Val Ala Gly Ser Cys Asn Asn Tyr
85           90           95

```

## (2) INFORMATION FOR SEQ ID NO:103:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 154 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

135

ATGACAGAGC AGCAGTGGAA TTTCGCGGGT ATCGAGGCCG CGGCAAGCGC AATCCAGGGA 60  
 AATGTCACGT CCATTCATTC CCTCCTTGAC GAGGGGAAGC AGTCCCTGAC CAAGCTCGCA 120  
 GCGGCCTGGG GCGGTAGCGG TTCGGAAGCG TACC 154

## (2) INFORMATION FOR SEQ ID NO:104:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 51 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

Met Thr Glu Gln Gln Trp Asn Phe Ala Gly Ile Glu Ala Ala Ala Ser  
 1 5 10 15  
 Ala Ile Gln Gly Asn Val Thr Ser Ile His Ser Leu Leu Asp Glu Gly  
 20 25 30  
 Lys Gln Ser Leu Thr Lys Leu Ala Ala Ala Trp Gly Gly Ser Gly Ser  
 35 40 45  
 Glu Ala Tyr  
 50

## (2) INFORMATION FOR SEQ ID NO:105:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 282 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

CGGTCGCGCA CTTCCAGGTG ACTATGAAAG TCGGCTTCCG NCTGGAGGAT TCCTGAACCT	60
TCAAGCGCGG CCGATAACTG AGGTGCATCA TTAAGCGACT TTTCCAGAAC ATCCTGACGC	120
GCTCGAAACG CGGCACAGCC GACGGTGGCT CCGNCGAGGC GCTGNCTCCA AAATCCCTGA	180
GACAATTCGN CGGGGGCGCC TACAAGGAAG TCGGTGCTGA ATTCGNCNG TATCTGGTCG	240
ACCTGTGTGG TCTGNAGCCG GACGAAGCGG TGCTCGACGT CG	282

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1565 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

GTATGCGGCC ACTGAAGTCG CCAATGCGGC GGCGGCCAGC TAAGCCAGGA ACAGTCGGCA	60
CGAGAAACCA CGAGAAATAG GGACACGTAA TGGTGGATTT CGGGGCGTTA CCACCGGAGA	120
TCAACTCCGC GAGGATGTAC GCCGGCCCGG GTTCGGCCTC GCTGGTGGCC GCGGCTCAGA	180
TGTGGGACAG CGTGGCGAGT GACCTGTTTT CGGCCGCGTC GGC GTTTCAG TCGGTGGTCT	240
GGGGTCTGAC GGTGGGGTCG TGGATAGGTT CGTCGGCGGG TCTGATGGTG GCGGCGGCCT	300
CGCCGTATGT GGC GTGGATG AGCGTCACCG CGGGGCAGGC CGAGCTGACC GCCGCCAGG	360
TCCGGGTTGC TCGGCGGCC TACGAGACGG CGTATGGCT GACGGTGCCC CCGCCGGTGA	420
TCGCCGAGAA CCGTGCTGAA CTGATGATTC TGATAGCGAC CAACCTCTTG GGGCAAAACA	480
CCCCGGCGAT CGCGGTCAAC GAGGCCGAAT ACGGCGAGAT GTGGGCCCAA GACGCCGCCG	540
CGATGTTTGG CTACGCCGCG GCGACGGCGA CGGCGACGGC GACGTTGCTG CCGTTCGAGG	600

AGGCGCCGGA GATGACCAGC GCGGGTGGGC TCCTCGAGCA GGCCGCCGCG GTCGAGGAGG	660
CCTCCGACAC CGCCGCGGCG AACCAGTTGA TGAACAATGT GCCCCAGGCG CTGCAACAGC	720
TGGCCCAGCC CACGCAGGGC ACCACGCCTT CTTCCAAGCT GGGTGGCCTG TGAAGACGG	780
TCTCGCCGCA TCGGTCGCCG ATCAGCAACA TGGTGTCAAT GGCCAACAAC CACATGTCAA	840
TGACCAACTC GGGTGTGTCA ATGACCAACA CCTTGAGCTC GATGTTGAAG GGCTTTGCTC	900
CGGCGGCGGC CGCCAGGCC GTGCAAACCG CGGCGCAAAA CGGGGTCCGG GCGATGAGCT	960
CGCTGGGCAG CTCGCTGGGT TCTTCGGGTC TGGGCGGTGG GGTGGCCGCC AACTTGGGTC	1020
GGGCGGCCTC GGTCGGTTCG TTGTCGGTGC CGCAGGCCTG GGCCGCGGCC AACCAGGCAG	1080
TCACCCCGGC GGC GCGGGCG CTGCCGCTGA CCAGCCTGAC CAGCGCCGCG GAAAGAGGGC	1140
CCGGGCAGAT GCTGGGCGGG CTGCCGGTGG GGCAGATGGG CGCCAGGGCC GGTGGTGGGC	1200
TCAGTGGTGT GCTGCGTGTT CCGCCGCGAC CCTATGTGAT GCCGCATTCT CCGGCGGCCG	1260
GCTAGGAGAG GGGGCGCAGA CTGTCGTTAT TTGACCAGTG ATCGGCGGTC TCGGTGTTTC	1320
CGCGGCCGCG TATGACAACA GTCAATGTGC ATGACAAGTT ACAGGTATTA GGTCCAGGTT	1380
CAACAAGGAG ACAGGCAACA TGGCCTCACG TTTTATGACG GATCCGCACG CGATGCGGGA	1440
CATGGCGGGC CGTTTTGAAG TGCACGCCCA GACGGTGGAG GACGAGGCTC GCCGGATGTG	1500
GGCGTCCGCG CAAAACATTT CCGGTGCGGG CTGGAGTGGC ATGGCCGAGG CGACCTCGCT	1560
AGACA	1565

## (2) INFORMATION FOR SEQ ID NO:107:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 391 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

Met	Val	Asp	Phe	Gly	Ala	Leu	Pro	Pro	Glu	Ile	Asn	Ser	Ala	Arg	Met	1	5	10	15
Tyr	Ala	Gly	Pro	Gly	Ser	Ala	Ser	Leu	Val	Ala	Ala	Ala	Gln	Met	Trp	20	25	30	
Asp	Ser	Val	Ala	Ser	Asp	Leu	Phe	Ser	Ala	Ala	Ser	Ala	Phe	Gln	Ser	35	40	45	
Val	Val	Trp	Gly	Leu	Thr	Val	Gly	Ser	Trp	Ile	Gly	Ser	Ser	Ala	Gly	50	55	60	
Leu	Met	Val	Ala	Ala	Ala	Ser	Pro	Tyr	Val	Ala	Trp	Met	Ser	Val	Thr	65	70	75	80
Ala	Gly	Gln	Ala	Glu	Leu	Thr	Ala	Ala	Gln	Val	Arg	Val	Ala	Ala	Ala	85	90	95	
Ala	Tyr	Glu	Thr	Ala	Tyr	Gly	Leu	Thr	Val	Pro	Pro	Pro	Val	Ile	Ala	100	105	110	
Glu	Asn	Arg	Ala	Glu	Leu	Met	Ile	Leu	Ile	Ala	Thr	Asn	Leu	Leu	Gly	115	120	125	
Gln	Asn	Thr	Pro	Ala	Ile	Ala	Val	Asn	Glu	Ala	Glu	Tyr	Gly	Glu	Met	130	135	140	
Trp	Ala	Gln	Asp	Ala	Ala	Ala	Met	Phe	Gly	Tyr	Ala	Ala	Ala	Thr	Ala	145	150	155	160
Thr	Ala	Thr	Ala	Thr	Leu	Leu	Pro	Phe	Glu	Glu	Ala	Pro	Glu	Met	Thr	165	170	175	
Ser	Ala	Gly	Gly	Leu	Leu	Glu	Gln	Ala	Ala	Ala	Val	Glu	Glu	Ala	Ser	180	185	190	
Asp	Thr	Ala	Ala	Ala	Asn	Gln	Leu	Met	Asn	Asn	Val	Pro	Gln	Ala	Leu	195	200	205	
Gln	Gln	Leu	Ala	Gln	Pro	Thr	Gln	Gly	Thr	Thr	Pro	Ser	Ser	Lys	Leu	210	215	220	

Gly Gly Leu Trp Lys Thr Val Ser Pro His Arg Ser Pro Ile Ser Asn  
 225 230 235 240  
 Met Val Ser Met Ala Asn Asn His Met Ser Met Thr Asn Ser Gly Val  
 245 250 255  
 Ser Met Thr Asn Thr Leu Ser Ser Met Leu Lys Gly Phe Ala Pro Ala  
 260 265 270  
 Ala Ala Ala Gln Ala Val Gln Thr Ala Ala Gln Asn Gly Val Arg Ala  
 275 280 285  
 Met Ser Ser Leu Gly Ser Ser Leu Gly Ser Ser Gly Leu Gly Gly Gly  
 290 295 300  
 Val Ala Ala Asn Leu Gly Arg Ala Ala Ser Val Gly Ser Leu Ser Val  
 305 310 315 320  
 Pro Gln Ala Trp Ala Ala Ala Asn Gln Ala Val Thr Pro Ala Ala Arg  
 325 330 335  
 Ala Leu Pro Leu Thr Ser Leu Thr Ser Ala Ala Glu Arg Gly Pro Gly  
 340 345 350  
 Gln Met Leu Gly Gly Leu Pro Val Gly Gln Met Gly Ala Arg Ala Gly  
 355 360 365  
 Gly Gly Leu Ser Gly Val Leu Arg Val Pro Pro Arg Pro Tyr Val Met  
 370 375 380  
 Pro His Ser Pro Ala Ala Gly  
 385 390

## (2) INFORMATION FOR SEQ ID NO:108:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 259 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

ACCAACACCT TGCACTCNAT GTTGAAGGGC TTAGCTCCGG CGGCGGCTCA GGCCGTGGAA 60  
 ACCGCGGCGG AAAACGGGGT CTGGGCAATG AGCTCGCTGG GCAGCCAGCT GGGTTCGTCTG 120  
 CTGGGTTCTT CGGGTCTGGG CGCTGGGGTG GCCGCCAACT TGGGTCGGGC GGCCTCGGTC 180  
 GGTTCGTTGT CGGTGCCGCC AGCATGGGCC GCGGCCAACC AGGCGGTCAC CCCGGCGGCG 240  
 CGGGCGCTGC CGCTGACCA 259

## (2) INFORMATION FOR SEQ ID NO:109:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 86 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

Thr Asn Thr Leu His Ser Met Leu Lys Gly Leu Ala Pro Ala Ala Ala  
 1 5 10 15  
 Gln Ala Val Glu Thr Ala Ala Glu Asn Gly Val Trp Ala Met Ser Ser  
 20 25 30  
 Leu Gly Ser Gln Leu Gly Ser Ser Leu Gly Ser Ser Gly Leu Gly Ala  
 35 40 45  
 Gly Val Ala Ala Asn Leu Gly Arg Ala Ala Ser Val Gly Ser Leu Ser  
 50 55 60  
 Val Pro Pro Ala Trp Ala Ala Ala Asn Gln Ala Val Thr Pro Ala Ala  
 65 70 75 80  
 Arg Ala Leu Pro Leu Thr  
 85

## (2) INFORMATION FOR SEQ ID NO:110:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1109 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

TACTTGAGAG AATTTGACCT GTTGCCGACG TTGTTTGCTG TCCATCATTG GTGCTAGTTA	60
TGGCCGAGCG GAAGGATTAT CGAAGTGGTG GACTTCGGGG CGTTACCACC GGAGATCAAC	120
TCCGCGAGGA TGTACGCCGG CCCGGGTTCG GCCTCGCTGG TGGCCGCCGC GAAGATGTGG	180
GACAGCGTGG CGAGTGACCT GTTTTCGGCC GCGTCGGCGT TTCAGTCGGT GGTCTGGGGT	240
CTGACGACGG GATCGTGGAT AGGTTCGTCG GCGGGTCTGA TGGTGGCGGC GGCCTCGCCG	300
TATGTGGCGT GGATGAGCGT CACCGCGGGG CAGGCCGAGC TGACCGCCGC CCAGGTCCGG	360
GTTGCTGCGG CGGCCTACGA GACGGCGTAT GGGCTGACGG TGCCCCCGCC GGTGATCGCC	420
GAGAACCGTG CTGAACTGAT GATTCTGATA GCGACCAACC TCTTGGGGCA AAACACCCCG	480
GCGATCGCGG TCAACGAGGC CGAATACGGG GAGATGTGGG CCCAAGACGC CGCCGCGATG	540
TTTGGCTACG CCGCCACGGC GCGGACGGCG ACCGAGGCGT TGCTGCCGTT CGAGGACGCC	600
CCACTGATCA CCAACCCCGG CGGGCTCCTT GAGCAGGCCG TCGCGGTCGA GGAGGCCATC	660
GACACCGCCG CGGCGAACCA GTTGATGAAC AATGTGCCCC AAGCGCTGCA ACAACTGGCC	720
CAGCCCACGA AAAGCATCTG GCCGTTGAC CAACTGAGTG AACTCTGGAA AGCCATCTCG	780
CCGCATCTGT CGCCGCTCAG CAACATCGTG TCGATGCTCA ACAACCACGT GTCGATGACC	840
AACTCGGGTG TGTCAATGGC CAGCACCTTG CACTCAATGT TGAAGGGCTT TGCTCCGGCG	900
GCGGCTCAGG CCGTGGAAC CGCGGCGCAA AACGGGGTCC AGGCGATGAG CTCGCTGGGC	960

AGCCAGCTGG GTTCGTCGCT GGGTTCTTCG GGTCTGGGCG CTGGGGTGGC CGCCAACTTG 1020  
 GGTCGGGCGG CCTCGGTCGG TTCGTTGTCG GTGCCGCAGG CCTGGGCCGC GGCCAACCAG 1080  
 GCGGTCACCC CGGCGGCGCG GGCCTGCC 1109

## (2) INFORMATION FOR SEQ ID NO:111:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 341 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

Val Val Asp Phe Gly Ala Leu Pro Pro Glu Ile Asn Ser Ala Arg Met  
 1 5 10 15  
 Tyr Ala Gly Pro Gly Ser Ala Ser Leu Val Ala Ala Ala Lys Met Trp  
 20 25 30  
 Asp Ser Val Ala Ser Asp Leu Phe Ser Ala Ala Ser Ala Phe Gln Ser  
 35 40 45  
 Val Val Trp Gly Leu Thr Thr Gly Ser Trp Ile Gly Ser Ser Ala Gly  
 50 55 60  
 Leu Met Val Ala Ala Ala Ser Pro Tyr Val Ala Trp Met Ser Val Thr  
 65 70 75 80  
 Ala Gly Gln Ala Glu Leu Thr Ala Ala Gln Val Arg Val Ala Ala Ala  
 85 90 95  
 Ala Tyr Glu Thr Ala Tyr Gly Leu Thr Val Pro Pro Pro Val Ile Ala  
 100 105 110  
 Glu Asn Arg Ala Glu Leu Met Ile Leu Ile Ala Thr Asn Leu Leu Gly  
 115 120 125

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Gln Asn Thr Pro Ala Ile Ala Val Asn Glu Ala Glu Tyr Gly Glu Met  
 130 135 140  
 Trp Ala Gln Asp Ala Ala Ala Met Phe Gly Tyr Ala Ala Thr Ala Ala  
 145 150 155 160  
 Thr Ala Thr Glu Ala Leu Leu Pro Phe Glu Asp Ala Pro Leu Ile Thr  
 165 170 175  
 Asn Pro Gly Gly Leu Leu Glu Gln Ala Val Ala Val Glu Glu Ala Ile  
 180 185 190  
 Asp Thr Ala Ala Ala Asn Gln Leu Met Asn Asn Val Pro Gln Ala Leu  
 195 200 205  
 Gln Gln Leu Ala Gln Pro Thr Lys Ser Ile Trp Pro Phe Asp Gln Leu  
 210 215 220  
 Ser Glu Leu Trp Lys Ala Ile Ser Pro His Leu Ser Pro Leu Ser Asn  
 225 230 235 240  
 Ile Val Ser Met Leu Asn Asn His Val Ser Met Thr Asn Ser Gly Val  
 245 250 255  
 Ser Met Ala Ser Thr Leu His Ser Met Leu Lys Gly Phe Ala Pro Ala  
 260 265 270  
 Ala Ala Gln Ala Val Glu Thr Ala Ala Gln Asn Gly Val Gln Ala Met  
 275 280 285  
 Ser Ser Leu Gly Ser Gln Leu Gly Ser Ser Leu Gly Ser Ser Gly Leu  
 290 295 300  
 Gly Ala Gly Val Ala Ala Asn Leu Gly Arg Ala Ala Ser Val Gly Ser  
 305 310 315 320  
 Leu Ser Val Pro Gln Ala Trp Ala Ala Ala Asn Gln Ala Val Thr Pro  
 325 330 335  
 Ala Ala Arg Ala Leu  
 340

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 1256 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

CATCGGAGGG AGTGATCACC ATGCTGTGGC ACGCAATGCC ACCGGAGNTA AATACCGCAC	60
GGCTGATGGC CGGCGCGGGT CCGGCTCCAA TGCTTGCGGC GGCCGCGGGA TGGCAGACGC	120
TTTCGGCGGC TCTGGACGCT CAGGCCGTCG AGTTGACCGC GCGCCTGAAC TCTCTGGGAG	180
AAGCCTGGAC TGGAGGTGGC AGCGACAAGG CGCTTGCGGC TGCAACGCCG ATGGTGGTCT	240
GGCTACAAAC CGCGTCAACA CAGGCCAAGA CCCGTGCGAT GCAGGCGACG GCGCAAGCCG	300
CGGCATACAC CCAGGCCATG GCCACGACGC CGTCGCTGCC GGAGATCGCC GCCAACCACA	360
TCACCCAGGC CGTCCTTACG GCCACCAACT TCTTCGGTAT CAACACGATC CCGATCGCGT	420
TGACCGAGAT GGATTATTTT ATCCGTATGT GGAACCAGGC AGCCCTGGCA ATGGAGGTCT	480
ACCAGGCCGA GACCGCGGTT AACACGCTTT TCGAGAAGCT CGAGCCGATG GCGTCGATCC	540
TTGATCCCGG CGCGAGCCAG AGCACGACGA ACCCGATCTT CGGAATGCCC TCCCCTGGCA	600
GCTCAACACC GGTGCGCCAG TTGCCGCCGG CGGCTACCCA GACCCTCGGC CAACTGGGTG	660
AGATGAGCGG CCCGATGCAG CAGCTGACCC AGCCGCTGCA GCAGGTGACG TCGTTGTTCA	720
GCCAGGTGGG CGGCACCGGC GCGGCAACC CAGCCGACGA GGAAGCCGCG CAGATGGGCC	780
TGCTCGGCAC CAGTCCGCTG TCGAACCATC CGCTGGCTGG TGGATCAGGC CCCAGCGCGG	840
GCGCGGGCCT GCTGCGCGCG GAGTCGCTAC CTGGCGCAGG TGGGTCGTTG ACCCGCACGC	900
CGCTGATGTC TCAGCTGATC GAAAAGCCGG TTGCCCCCTC GGTGATGCCG GCGGCTGCTG	960
CCGGATCGTC GGCGACGGGT GCGCCGCTC CGGTGGGTGC GGGAGCGATG GGCCAGGGTG	1020

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CGCAATCCGG CGGCTCCACC AGGCCGGGTC TGGTCGCGCC GGCACCGCTC GCGCAGGAGC	1080
GTGAAGAAGA CGACGAGGAC GACTGGGACG AAGAGGACGA CTGGTGAGCT CCCGTAATGA	1140
CAACAGACTT CCGGCCACC CGGGCCGGAA GACTTGCCAA CATTTTGGCG AGGAAGGTAA	1200
AGAGAGAAAG TAGTCCAGCA TGGCAGAGAT GAAGACCGAT GCCGCTACCC TCGCGC	1256

## (2) INFORMATION FOR SEQ ID NO:113:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 432 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

CTAGTGGATG GGACCATGGC CATTTTCTGC AGTCTCACTG CCTTCTGTGT TGACATTTTG	60
GCACGCCGGC GGAAACGAAG CACTGGGGTC GAAGAACGGC TCGCTGCCA TATCGTCCGG	120
AGCTTCCATA CCTTCGTGCG GCCGGAAGAG CTTGTCGTAG TCGGCCGCCA TGACAACCTC	180
TCAGAGTGCG CTCAAACGTA TAAACACGAG AAAGGGCGAG ACCGACGGAA GGTCGAACTC	240
GCCCATCCC GTGTTTCGCT ATTCTACGCG AACTCGGCGT TGCCCTATGC GAACATCCCA	300
GTGACGTTGC CTTGGTTCGA AGCCATTGCC TGACCGGCTT CGCTGATCGT CCGCGCCAGG	360
TTCTGCAGCG CGTTGTTTCTAG CTCGGTAGCC GTGGCGTCCC ATTTTGTCTG GACACCCTGG	420
TACGCCTCCG AA	432

## (2) INFORMATION FOR SEQ ID NO:114:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 368 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

Met	Leu	Trp	His	Ala	Met	Pro	Pro	Glu	Xaa	Asn	Thr	Ala	Arg	Leu	Met
1				5					10					15	
Ala	Gly	Ala	Gly	Pro	Ala	Pro	Met	Leu	Ala	Ala	Ala	Ala	Gly	Trp	Gln
			20					25					30		
Thr	Leu	Ser	Ala	Ala	Leu	Asp	Ala	Gln	Ala	Val	Glu	Leu	Thr	Ala	Arg
		35					40					45			
Leu	Asn	Ser	Leu	Gly	Glu	Ala	Trp	Thr	Gly	Gly	Gly	Ser	Asp	Lys	Ala
	50						55					60			
Leu	Ala	Ala	Ala	Thr	Pro	Met	Val	Val	Trp	Leu	Gln	Thr	Ala	Ser	Thr
65					70					75					80
Gln	Ala	Lys	Thr	Arg	Ala	Met	Gln	Ala	Thr	Ala	Gln	Ala	Ala	Ala	Tyr
				85					90						95
Thr	Gln	Ala	Met	Ala	Thr	Thr	Pro	Ser	Leu	Pro	Glu	Ile	Ala	Ala	Asn
			100					105					110		
His	Ile	Thr	Gln	Ala	Val	Leu	Thr	Ala	Thr	Asn	Phe	Phe	Gly	Ile	Asn
			115					120					125		
Thr	Ile	Pro	Ile	Ala	Leu	Thr	Glu	Met	Asp	Tyr	Phe	Ile	Arg	Met	Trp
			130				135					140			
Asn	Gln	Ala	Ala	Leu	Ala	Met	Glu	Val	Tyr	Gln	Ala	Glu	Thr	Ala	Val
145					150					155					160
Asn	Thr	Leu	Phe	Glu	Lys	Leu	Glu	Pro	Met	Ala	Ser	Ile	Leu	Asp	Pro
				165					170					175	
Gly	Ala	Ser	Gln	Ser	Thr	Thr	Asn	Pro	Ile	Phe	Gly	Met	Pro	Ser	Pro
			180					185					190		
Gly	Ser	Ser	Thr	Pro	Val	Gly	Gln	Leu	Pro	Pro	Ala	Ala	Thr	Gln	Thr
			195				200						205		

147

Leu Gly Gln Leu Gly Glu Met Ser Gly Pro Met Gln Gln Leu Thr Gln  
 210 215 220  
 Pro Leu Gln Gln Val Thr Ser Leu Phe Ser Gln Val Gly Gly Thr Gly  
 225 230 235 240  
 Gly Gly Asn Pro Ala Asp Glu Glu Ala Ala Gln Met Gly Leu Leu Gly  
 245 250 255  
 Thr Ser Pro Leu Ser Asn His Pro Leu Ala Gly Gly Ser Gly Pro Ser  
 260 265 270  
 Ala Gly Ala Gly Leu Leu Arg Ala Glu Ser Leu Pro Gly Ala Gly Gly  
 275 280 285  
 Ser Leu Thr Arg Thr Pro Leu Met Ser Gln Leu Ile Glu Lys Pro Val  
 290 295 300  
 Ala Pro Ser Val Met Pro Ala Ala Ala Ala Gly Ser Ser Ala Thr Gly  
 305 310 315 320  
 Gly Ala Ala Pro Val Gly Ala Gly Ala Met Gly Gln Gly Ala Gln Ser  
 325 330 335  
 Gly Gly Ser Thr Arg Pro Gly Leu Val Ala Pro Ala Pro Leu Ala Gln  
 340 345 350  
 Glu Arg Glu Glu Asp Asp Glu Asp Asp Trp Asp Glu Glu Asp Asp Trp  
 355 360 365

## (2) INFORMATION FOR SEQ ID NO:115:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 12 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

Met Ala Glu Met Lys Thr Asp Ala Ala Thr Leu Ala  
1                      5                      10

(2) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 396 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

GATCTCCGGC GACCTGAAAA CCCAGATCGA CCAGGTGGAG TCGACGGCAG GTTCGTTGCA	60
GGGCCAGTGG CGCGGCGCGG CGGGGACGGC CGCCCAGGCC GCGGTGGTGC GCTTCCAAGA	120
AGCAGCCAAT AAGCAGAAGC AGGAACTCGA CGAGATCTCG ACGAATATTC GTCAGGCCGG	180
CGTCCAATAC TCGAGGGCCG ACGAGGAGCA GCAGCAGGCG CTGTCCTCGC AAATGGGCTT	240
CTGACCCGCT AATACGAAAA GAAACGGAGC AAAACATGA CAGAGCAGCA GTGGAATTTC	300
GCGGGTATCG AGGCCGCGGC AAGCGCAATC CAGGGAAATG TCACGTCCAT TCATTCCCTC	360
CTTGACGAGG GGAAGCAGTC CCTGACCAAG CTCGCA	396

(2) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 80 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

149

Ile Ser Gly Asp Leu Lys Thr Gln Ile Asp Gln Val Glu Ser Thr Ala  
 1                      5                      10                      15  
 Gly Ser Leu Gln Gly Gln Trp Arg Gly Ala Ala Gly Thr Ala Ala Gln  
                     20                      25                      30  
 Ala Ala Val Val Arg Phe Gln Glu Ala Ala Asn Lys Gln Lys Gln Glu  
                     35                      40                      45  
 Leu Asp Glu Ile Ser Thr Asn Ile Arg Gln Ala Gly Val Gln Tyr Ser  
                     50                      55                      60  
 Arg Ala Asp Glu Glu Gln Gln Gln Ala Leu Ser Ser Gln Met Gly Phe  
                     65                      70                      75                      80

## (2) INFORMATION FOR SEQ ID NO:118:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 387 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

GTGGATCCCG ATCCCGTGTT TCGCTATTCT ACGCGAACTC GGC GTTGCCC TATGCGAACA	60
TCCCAGTGAC GTTGCCCTCG GTCGAAGCCA TTGCCTGACC GGCTTCGCTG ATCGTCCGCG	120
CCAGGTTCTG CAGCGCGTTG TTCAGCTCGG TAGCCGTGGC GTCCCATTTT TGCTGGACAC	180
CCTGGTACGC CTCCGAACCG CTACCGCCCC AGGCCGCTGC GAGCTTGGTC AGG GACTGCT	240
TCCCCTCGTC AAGGAGGGAA TGAATGGACG TGACATTTCC CTGGATTGCG CTTGCCGCGG	300
CCTCGATACC CGCGAAATTC CACTGCTGCT CTGTCATGTT TTTGCTCCGT TTCTTTTCGT	360
ATTAGCGGGT CAGAAGCCCA TTTGCGA	387

150

## (2) INFORMATION FOR SEQ ID NO:119:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 272 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

```

CGGCACGAGG ATCTCGGTTG GCCCAACGGC GCTGGCGAGG GCTCCGTTCC GGGGGCGAGC      60
TGCGCGCCGG ATGCTTCCTC TGCCCGCAGC CGCGCCTGGA TGGATGGACC AGTTGCTACC      120
TTCCCGACGT TTCGTTCCGT GTCTGTGCGA TAGCGGTGAC CCCGGCGCGC ACGTCGGGAG      180
TGTTGGGGGG CAGGCCGGGT CGGTGGTTCG GCCGGGGACG CAGACGGTCT GGACGGAACG      240
GGCGGGGGTT CGCCGATTGG CATCTTTGCC CA                                     272

```

## (2) INFORMATION FOR SEQ ID NO:120:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

```

Asp Pro Val Asp Ala Val Ile Asn Thr Thr Cys Asn Tyr Gly Gln Val
1           5           10           15
Val Ala Ala Leu
                20

```

## (2) INFORMATION FOR SEQ ID NO:121:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 15 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

Ala	Val	Glu	Ser	Gly	Met	Leu	Ala	Leu	Gly	Thr	Pro	Ala	Pro	Ser
1				5					10					15

(2) INFORMATION FOR SEQ ID NO:122:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 19 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

Ala	Ala	Met	Lys	Pro	Arg	Thr	Gly	Asp	Gly	Pro	Leu	Glu	Ala	Ala	Lys
1				5					10					15	

Glu Gly Arg

(2) INFORMATION FOR SEQ ID NO:123:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 15 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

Tyr	Tyr	Trp	Cys	Pro	Gly	Gln	Pro	Phe	Asp	Pro	Ala	Trp	Gly	Pro
1				5					10					15

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

Asp	Ile	Gly	Ser	Glu	Ser	Thr	Glu	Asp	Gln	Gln	Xaa	Ala	Val
1				5					10				

(2) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 13 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

Ala	Glu	Glu	Ser	Ile	Ser	Thr	Xaa	Glu	Xaa	Ile	Val	Pro
1				5					10			

(2) INFORMATION FOR SEQ ID NO:126:

(i) SEQUENCE CHARACTERISTICS:

153

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

Asp	Pro	Glu	Pro	Ala	Pro	Pro	Val	Pro	Thr	Thr	Ala	Ala	Ser	Pro	Pro
1				5					10					15	

Ser

(2) INFORMATION FOR SEQ ID NO:127:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 15 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

Ala	Pro	Lys	Thr	Tyr	Xaa	Glu	Glu	Leu	Lys	Gly	Thr	Asp	Thr	Gly
1				5					10					15

(2) INFORMATION FOR SEQ ID NO:128:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 30 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

Asp	Pro	Ala	Ser	Ala	Pro	Asp	Val	Pro	Thr	Ala	Ala	Gln	Leu	Thr	Ser
1				5					10					15	
Leu	Leu	Asn	Ser	Leu	Ala	Asp	Pro	Asn	Val	Ser	Phe	Ala	Asn		
		20						25					30		

(2) INFORMATION FOR SEQ ID NO:129:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 22 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

Asp	Pro	Pro	Asp	Pro	His	Gln	Xaa	Asp	Met	Thr	Lys	Gly	Tyr	Tyr	Pro
1				5					10					15	
Gly	Gly	Arg	Arg	Xaa	Phe										
		20													

(2) INFORMATION FOR SEQ ID NO:130:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 7 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

Asp	Pro	Gly	Tyr	Thr	Pro	Gly
1				5		

## (2) INFORMATION FOR SEQ ID NO:131:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 10 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

## (ix) FEATURE:

(D) OTHER INFORMATION: /note= "The Second Residue Can Be Either a Pro or Thr"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

Xaa	Xaa	Gly	Phe	Thr	Gly	Pro	Gln	Phe	Tyr
1				5					10

## (2) INFORMATION FOR SEQ ID NO:132:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 9 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

## (ix) FEATURE:

(D) OTHER INFORMATION: /note= "The Third Residue Can Be Either a Gln or Leu"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

Xaa	Pro	Xaa	Val	Thr	Ala	Tyr	Ala	Gly
1				5				

## (2) INFORMATION FOR SEQ ID NO:133:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 9 amino acids

156

- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

Xaa Xaa Xaa Glu Lys Pro Phe Leu Arg  
1 5

(2) INFORMATION FOR SEQ ID NO:134:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 15 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

Xaa Asp Ser Glu Lys Ser Ala Thr Ile Lys Val Thr Asp Ala Ser  
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:135:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 15 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

Ala Gly Asp Thr Xaa Ile Tyr Ile Val Gly Asn Leu Thr Ala Asp

157

1 5 10 15

## (2) INFORMATION FOR SEQ ID NO:136:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:

Ala Pro Glu Ser Gly Ala Gly Leu Gly Gly Thr Val Gln Ala Gly  
1 5 10 15

## (2) INFORMATION FOR SEQ ID NO:137:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

Xaa Tyr Ile Ala Tyr Xaa Thr Thr Ala Gly Ile Val Pro Gly Lys Ile  
1 5 10 15

Asn Val His Leu Val  
20

Claims

1. A polypeptide comprising an immunogenic portion of a soluble *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen has an N-terminal sequence selected from the group consisting of:

- (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Cys-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu; (SEQ ID No. 120)
- (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser; (SEQ ID No. 121)
- (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg; (SEQ ID No. 122)
- (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro; (SEQ ID No. 123)
- (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val; (SEQ ID No. 124)
- (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro; (SEQ ID No. 125)
- (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Thr-Ala-Ala-Ser-Pro-Pro-Ser; (SEQ ID No. 126)
- (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-Gly; (SEQ ID No. 127)
- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Leu-Thr-Ser-Leu-Leu-Asn-Ser-Leu-Ala-Asp-Pro-Asn-Val-Ser-Phe-Ala-Asn; (SEQ ID No. 128) and
- (j) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 136)

wherein Xaa may be any amino acid.

2. A polypeptide comprising an immunogenic portion of an *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative

substitutions and/or modifications, wherein said antigen has an N-terminal sequence selected from the group consisting of:

- (a) Asp-Pro-Pro-Asp-Pro-His-Gln-Xaa-Asp-Met-Thr-Lys-Gly-Tyr-Tyr-Pro-Gly-Gly-Arg-Arg-Xaa-Phe; (SEQ ID No. 129) and
- (b) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No. 137), wherein Xaa may be any amino acid.

3. A polypeptide comprising an immunogenic portion of a soluble *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos.: 1, 2, 4-10, 13-25, 52, 99 and 101, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 1, 2, 4-10, 13-25, 52, 99 and 101 or a complement thereof under moderately stringent conditions.

4. A polypeptide comprising an immunogenic portion of a *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos.: 26-51, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 26-51 or a complement thereof under moderately stringent conditions.

5. A DNA molecule comprising a nucleotide sequence encoding a polypeptide according to any one of claims 1-4.

6. An expression vector comprising a DNA molecule according to claim 5.

7. A host cell transformed with an expression vector according to claim 6.

8. The host cell of claim 7 wherein the host cell is selected from the group consisting of *E. coli*, yeast and mammalian cells.
9. A pharmaceutical composition comprising one or more polypeptides according to any one of claims 1-4 and a physiologically acceptable carrier.
10. A pharmaceutical composition comprising one or more DNA molecules according to claim 5 and a physiologically acceptable carrier.
11. A pharmaceutical composition comprising one or more DNA sequences recited in SEQ ID Nos.: 3, 11 and 12; and a physiologically acceptable carrier.
12. A vaccine comprising one or more polypeptides according to any one of claims 1-4 and a non-specific immune response enhancer.
13. A vaccine comprising:  
a polypeptide having an N-terminal sequence selected from the group consisting of sequences recited in SEQ ID NO: 134 and 135; and  
a non-specific immune response enhancer.
14. A vaccine comprising:  
one or more polypeptides encoded by a DNA sequence selected from the group consisting of SEQ ID Nos.: 3, 11 and 12, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 3, 11 and 12; and  
a non-specific immune response enhancer.
15. The vaccine of claims 12-14 wherein the non-specific immune response enhancer is an adjuvant.
16. A vaccine comprising one or more DNA molecules according to claim 5 and a non-specific immune response enhancer.

17. A vaccine comprising one or more DNA sequences recited in SEQ ID Nos.: 3, 11 and 12; and a non-specific immune response enhancer.

18. The vaccine of claims 16 or 17 wherein the non-specific immune response enhancer is an adjuvant.

19. A method for inducing protective immunity in a patient, comprising administering to a patient a pharmaceutical composition according to any one of claims 9-11.

20. A method for inducing protective immunity in a patient, comprising administering to a patient a vaccine according to any one of claims 12-18.

21. A fusion protein comprising two or more polypeptides according to any one of claims 1-4.

22. A fusion protein comprising one or more polypeptides according to any one of claims 1-4 and ESAT-6.

23. A pharmaceutical composition comprising a fusion protein according to claim 21 or 22 and a physiologically acceptable carrier.

24. A vaccine comprising a fusion protein according to claims 21 or 22 and a non-specific immune response enhancer.

25. The vaccine of claim 24 wherein the non-specific immune response enhancer is an adjuvant.

26. A method for inducing protective immunity in a patient, comprising administering to a patient a pharmaceutical composition according to claim 23.

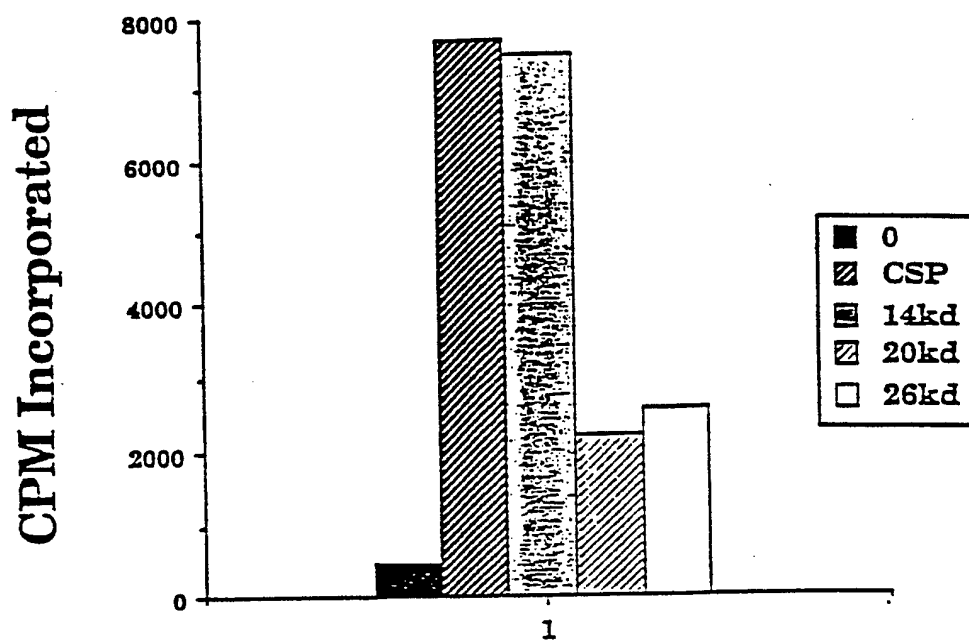
27. A method for inducing protective immunity in a patient, comprising administering to a patient a vaccine according to claims 24 or 25.

28. A method for detecting tuberculosis in a patient, comprising:
- (a) contacting dermal cells of a patient with one or more polypeptides according to any one of claims 1-4; and
  - (b) detecting an immune response on the patient's skin and therefrom detecting tuberculosis in the patient.
29. A method for detecting tuberculosis in a patient, comprising:
- (a) contacting dermal cells of a patient with a polypeptide having an N-terminal sequence selected from the group consisting of sequences recited in SEQ ID NO: 134 and 135; and
  - (b) detecting an immune response on the patient's skin and therefrom detecting tuberculosis in the patient.
30. A method for detecting tuberculosis in a patient, comprising:
- (a) contacting dermal cells of a patient with one or more polypeptides encoded by a DNA sequence selected from the group consisting of SEQ ID Nos.: 3, 11 and 12, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 3, 11 and 12; and
  - (b) detecting an immune response on the patient's skin and therefrom detecting tuberculosis in the patient.
31. The method of any one of claims 28-30 wherein the immune response is induration.
32. A diagnostic kit comprising:
- (a) a polypeptide according to any one of claims 1-4; and
  - (b) apparatus sufficient to contact said polypeptide with the dermal cells of a patient.

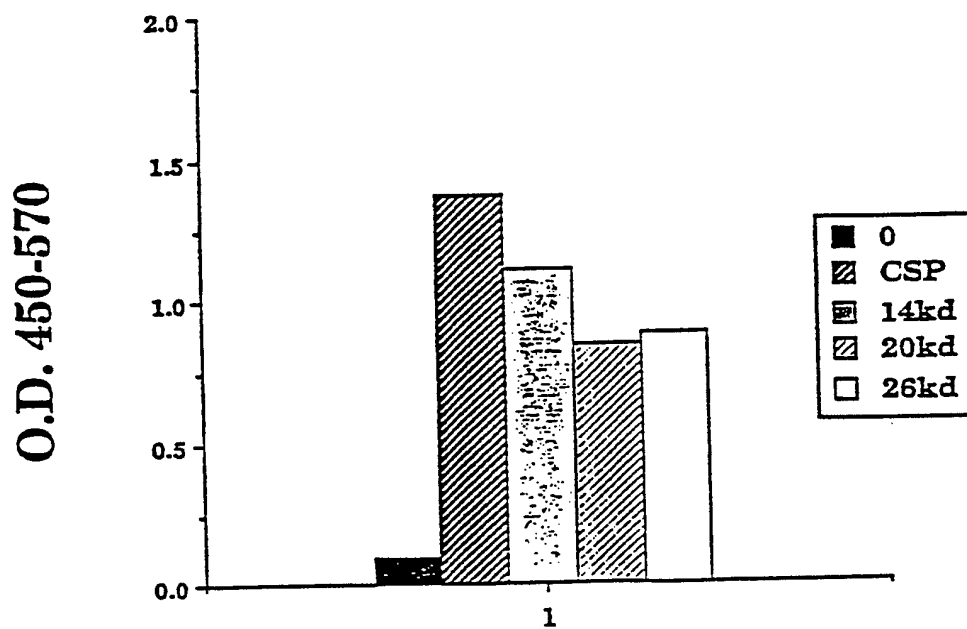
33. A diagnostic kit comprising:
- (a) a polypeptide having an N-terminal sequence selected from the group consisting of sequences recited in SEQ ID NO: 134 and 135; and
  - (b) apparatus sufficient to contact said polypeptide with the dermal cells of a patient.
34. A diagnostic kit comprising:
- (a) a polypeptide encoded by a DNA sequence selected from the group consisting of SEQ ID Nos.: 3, 11 and 12, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 3, 11 and 12; and
  - (b) apparatus sufficient to contact said polypeptide with the dermal cells of a patient.

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# D7 T Cell Proliferation

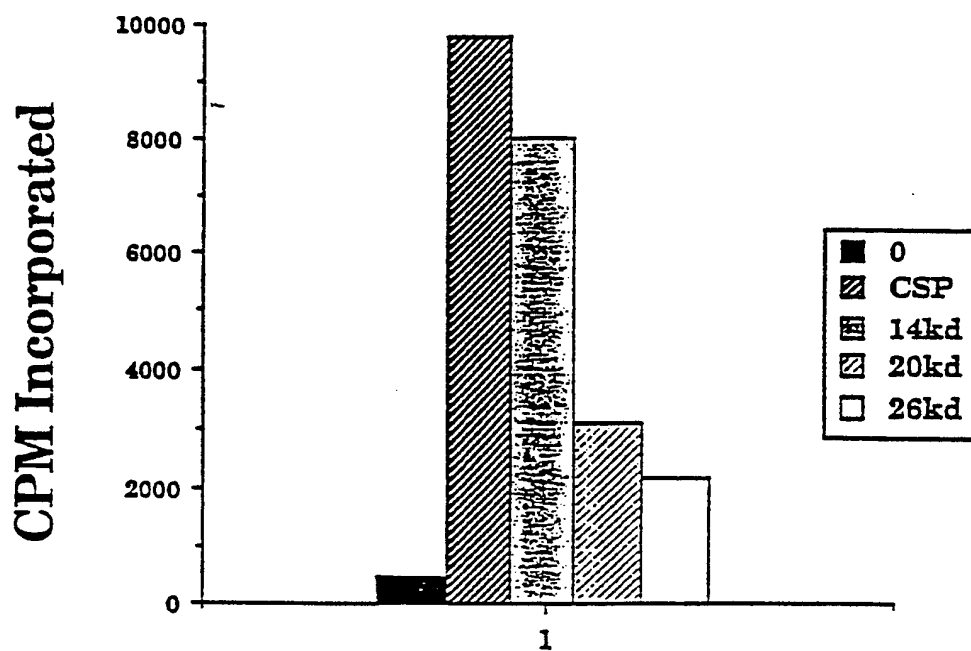


## D7 IFN $\gamma$

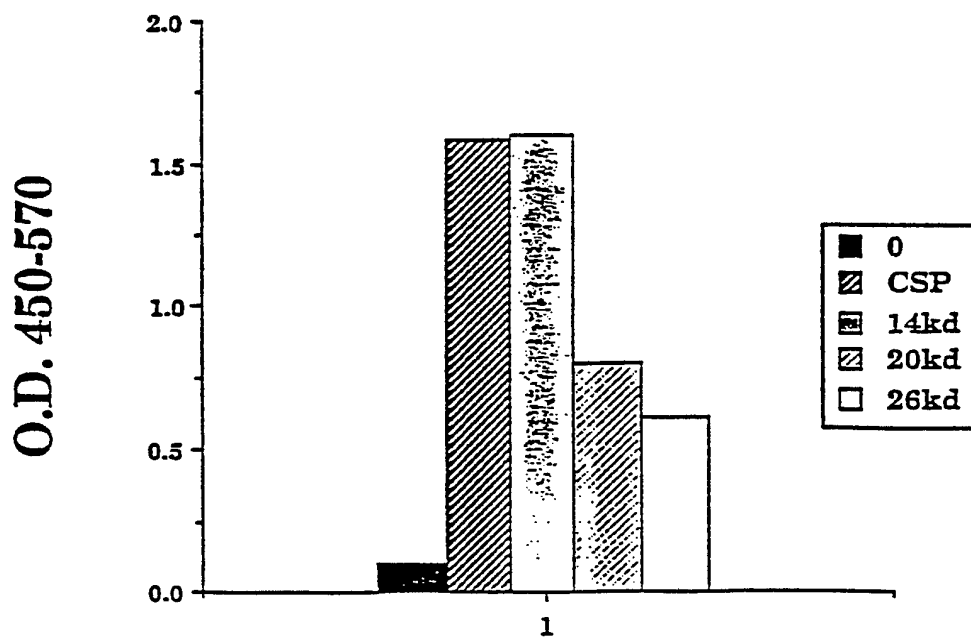
*Fig. 1A*

2/3

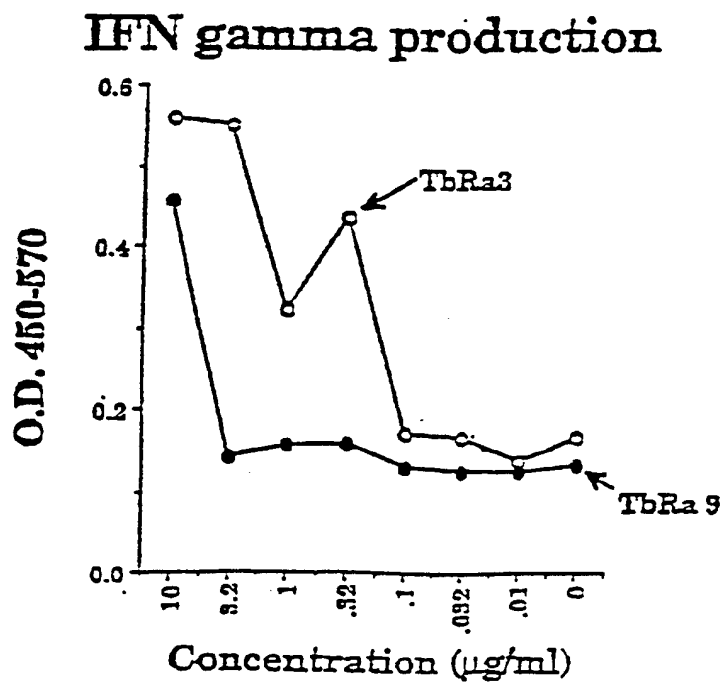
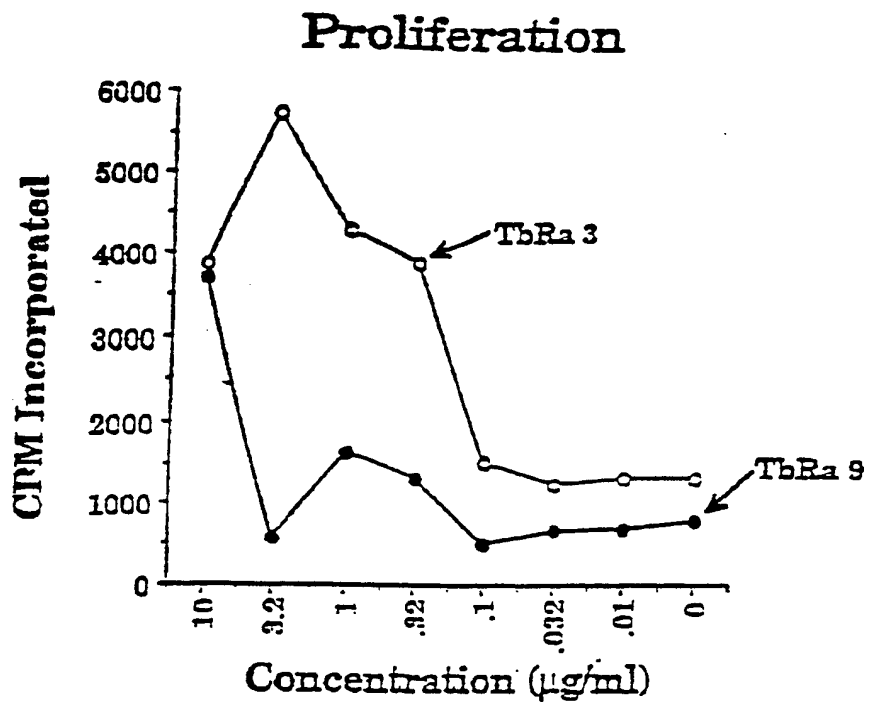
# D160 T Cell Proliferation



## D160 IFN $\gamma$

*Fig. 1B*

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*Fig. 2*



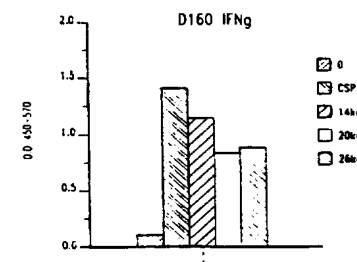
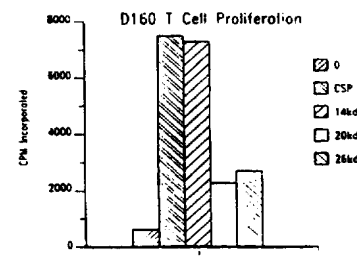
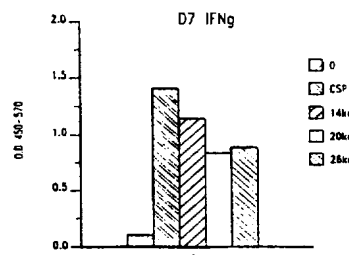
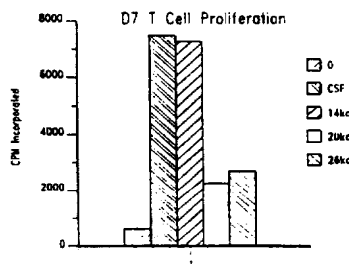
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<b>(21) International Application Number:</b> PCT/US96/14674 <b>(22) International Filing Date:</b> 30 August 1996 (30.08.96)		<b>(74) Agents:</b> MAKI, David, J. et al.; Seed and Berry L.L.P., 6300 Columbia Center, 701 Fifth Avenue, Seattle, WA 98104-7092 (US).	
<b>(30) Priority Data:</b> 08/523,436 1 September 1995 (01.09.95) US 08/533,634 22 September 1995 (22.09.95) US 08/620,874 22 March 1996 (22.03.96) US 08/659,683 5 June 1996 (05.06.96) US 08/680,574 12 July 1996 (12.07.96) US		<b>(81) Designated States:</b> AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
<b>(71) Applicant:</b> CORIXA CORPORATION [US/US]; Suite 464, 1124 Columbia Street, Seattle, WA 98104 (US). <b>(72) Inventors:</b> REED, Steven, G.; 2843 - 122nd Pine Place N.E., Bellevue, WA 98005 (US). SKEIKY, Yasir, A., W.; 8327 - 25th Avenue N.W., Seattle, WA 98117 (US). DILLON, Davin, C.; 21607 N.E. 24th Street, Redmond, WA 98053 (US). CAMPOS-NETO, Antonio; 9308 N.E. Midship Court, Bainbridge Island, WA 98110 (US). HOUGHTON, Raymond; 2636 - 242nd Place S.E., Bothell, WA 98021 (US). VEDVICK, Thomas, H.; 1301 Spring Street, Seattle, WA 98104 (US). TWARDZIK, Daniel, R.; 10195 South Beach Drive, Bainbridge Island, WA 98110 (US).		<b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> <b>(88) Date of publication of the international search report:</b> 17 July 1997 (17.07.97)	

**(54) Title:** COMPOUNDS AND METHODS FOR IMMUNOTHERAPY AND DIAGNOSIS OF TUBERCULOSIS

**(57) Abstract**

Compounds and methods for inducing protective immunity against tuberculosis are disclosed. The compounds provided include polypeptides that contain at least one immunogenic portion of one or more *M. tuberculosis* proteins and DNA molecules encoding such polypeptides. Such compounds may be formulated into vaccines and/or pharmaceutical compositions for immunization against *M. tuberculosis* infection, or may be used for the diagnosis of tuberculosis.



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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 96/14674

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C12N15/31 C07K14/35 A61K38/16 C12N15/62 G01N33/569  
C12Q1/68 C12N5/10 C12N1/21 //A61K39/04,  
(C12N1/21, C12R1:19)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 95 01440 A (STATENS SERUMINSTITUT ;HASLOEV KAARE (DK); ANDERSEN AASE BENGAARD) 12 January 1995</p> <p>see abstract see page 1, line 1-30 see page 4, line 8-31 see page 6, line 22 - page 7, line 21 see page 11, line 18 - page 12, line 31 see page 17, line 8-24 see page 24, line 18-25; figure 1 see page 36 - page 43; examples 2-5 see claims</p> <p style="text-align: center;">--- -/--</p>	<p>1,3-9, 12,15, 19,20, 28,31,32</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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- \*&\* document member of the same patent family

Date of the actual completion of the international search

3 March 1997

Date of mailing of the international search report

04. 06. 97

Name and mailing address of the ISA

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Macchia, G

# INTERNATIONAL SEARCH REPORT

Internat Application No  
PCT/US 96/14674

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 95 01441 A (STATENS SERUMSINSTITUT ;ANDERSEN PETER (DK); ANDERSEN AASE BENGAAR) 12 January 1995</p> <p>see abstract see page 9, line 3 - page 20, line 31 see page 25, line 1-25 see page 32, line 6 - page 35, line 6 see claims</p> <p style="text-align: center;">---</p>	<p>1,3-10, 12,15, 16,18, 22-27</p>
A	<p>VACCINE, vol. 12, no. 16, 1994, pages 1537-1540, XP002026338 LOWRIE ET AL.: "Towards a DNA vaccine against tuberculosis" see abstract see page 1539, left-hand column, paragraph 4</p> <p style="text-align: center;">---</p>	<p>10,16,18</p>
A	<p>INFECTION AND IMMUNITY, vol. 57, no. 1, January 1989, pages 283-288, XP002026408 YAMAGUCHI ET AL.: "Cloning and characterization of the gene for immunogenic protein MpB64 of mycobacterium bovis BCG"</p> <p style="text-align: center;">---</p>	
A	<p>ANN. INST. PASTEUR/MICROBIOL., vol. 136B, 1985, pages 235-248, XP002026409 ROMAIN ET AL.: "Preparation of Tuberculin antigen L"</p> <p style="text-align: center;">---</p>	
A	<p>WO 92 21758 A (PASTEUR INSTITUT) 10 December 1992</p> <p style="text-align: center;">---</p>	
A	<p>AUSUBEL ET AL.: "Current Protocols in Molecular Biology" 1993, WILEY &amp; SONS, US, NEW YORK XP002026411 see page 10.19.1 - page 10.19.12</p> <p style="text-align: center;">---</p>	
A	<p>INFECTION AND IMMUNITY, vol. 55, no. 6, June 1987, pages 1421-1425, XP002026410 YOUNG ET AL.: "Screening of a recombinant mycobacterial DNA library with polyclonal antiserum and molecular weight analysis of expressed antigens"</p> <p style="text-align: center;">---</p>	
A	<p>WO 94 00493 A (KAPOOR ARCHANA ;MUNSHI ANIL (US)) 6 January 1994</p> <p style="text-align: center;">-----</p>	

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/ 14674

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19,20,26-28,31  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although these claims are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

51 inventions \* see continuation-sheets PCT/ISA/210 \*

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1,3-10,12,15,16,18-28,31,32 all partially

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/ 14674

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

- 1) claims 1, 3-10, 12, 15, 16, 18-28, 31, 32 all partially:  
a polypeptide comprising an immunogenic portion of a soluble M. tuberculosis antigen or a variant, having an N-terminal aminoacid sequence as in Seq. ID:120, a DNA molecule encoding said polypeptide as in Seq. ID:101, overlapping or adjacent DNA molecule as in Seq. ID:31, 32, 33, 51 and encoded polypeptides, an expression vector comprising said DNA molecules, an host transformed with said expression vector, pharmaceutical and vaccine compositions comprising said polypeptides or said DNA molecules, fusion protein comprising said polypeptides, a diagnostic kit comprising said polypeptides.
- 2) claims 1, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:121.
- 3) claims 1, 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:122 and 25.
- 4) claims 1, 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:123 and 24.
- 5) claims 1, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:124.
- 6) claims 1, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:125.
- 7) claims 1, 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:126 and 52.
- 8) claims 1, 5-12, 14-28, 30-32, 34 all partially:  
same as invention 1 but for Seq. ID:127 and 3.
- 9) claims 1, 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:128, 99, 1 and 21.
- 10) claims 1, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:136.

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/ 14674

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

11) claims 2, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:129.

12) claims 2, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:137.

13) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:2.

14) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:4 and 17.

15) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:5, 14 and 18.

16) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:6.

17) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:7.

18) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:8.

19) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:9.

20) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:10 and 13.

21) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:15.

22) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:16.

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/ 14674

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

23) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:19.

24) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:20.

25) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:22.

26) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:23.

27) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:26.

28) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:27.

29) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:28.

30) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:29.

31) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:30.

32) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:34.

33) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:35.

34) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:36.

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/ 14674

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

35) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:37.

36) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:38.

37) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:39.

38) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:40.

39) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:41.

40) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:42.

41) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:43 and 44.

42) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:45.

43) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:46.

44) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:47.

45) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:48.

46) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:49.

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/ 14674

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

47) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:  
same as invention 1 but for Seq. ID:50.

48) claims 11, 14, 15, 17-20, 30, 31, 34 all partially:  
pharmaceutical and vaccine compositions comprising a DNA molecule as  
in Seq. ID:11 or the encoded polypeptide, a diagnostic kit comprising said  
polypeptide.

49) claims 11, 14, 15, 17-20, 30, 31, 34 all partially:  
same as invention 50 but for Seq. ID:12.

50) claims 13, 15, 20, 29, 31, 33 all partially:  
vaccine comprising a polypeptide whose N-terminal sequence is as Seq.  
ID:134, a diagnostic kit comprising said polypeptide.

51) claims 13, 15, 20, 29, 31, 33 all partially:  
same as invention 52 but for Seq. ID:135.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/14674

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO 9501441 A	12-01-95	AU 7068894 A CA 2165949 A EP 0706571 A	24-01-95 12-01-95 17-04-96
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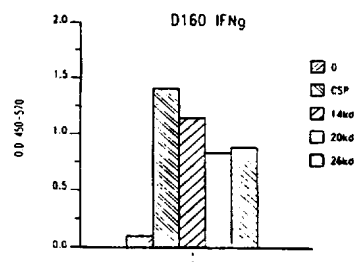
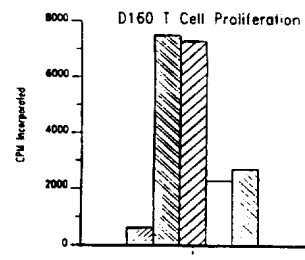
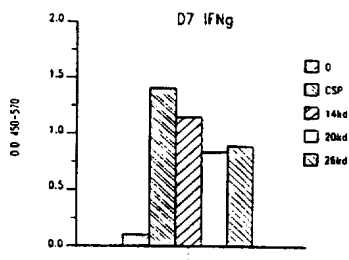
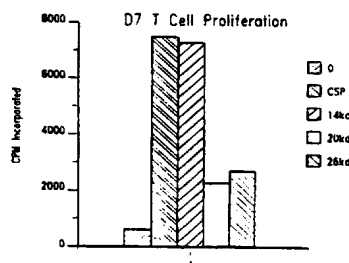
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(51) International Patent Classification <sup>6</sup> : <b>C12N 15/31, C07K 14/35, A61K 38/16, C12N 15/62, G01N 33/569, C12Q 1/68, C12N 5/10, 1/21 // A61K 39/04, (C12N 1/21, 1:19)</b>		A2	(11) International Publication Number: <b>WO 97/09428</b>
(21) International Application Number: <b>PCT/US96/14674</b>		(74) Agents: MAKI, David, J. et al.; Seed and Berry L.L.P., 6300 Columbia Center, 701 Fifth Avenue, Seattle, WA 98104- 7092 (US).	
(22) International Filing Date: <b>30 August 1996 (30.08.96)</b>		(43) International Publication Date: <b>13 March 1997 (13.03.97)</b>	
(30) Priority Data: 08/523,436 1 September 1995 (01.09.95) US 08/533,634 22 September 1995 (22.09.95) US 08/620,874 22 March 1996 (22.03.96) US 08/659,683 5 June 1996 (05.06.96) US 08/680,574 12 July 1996 (12.07.96) US		(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(71) Applicant: CORIXA CORPORATION [US/US]; Suite 464, 1124 Columbia Street, Seattle, WA 98104 (US).		<p><b>Published</b></p> <p><i>Without international search report and to be republished upon receipt of that report.</i></p>	
(72) Inventors: REED, Steven, G.; 2843 - 122nd Pine Place N.E., Bellevue, WA 98005 (US). SKEIKY, Yasir, A., W.; 8327 - 25th Avenue N.W., Seattle, WA 98117 (US). DILLON, Davin, C.; 21607 N.E. 24th Street, Redmond, WA 98053 (US). CAMPOS-NETO, Antonio; 9308 N.E. Midship Court, Bainbridge Island, WA 98110 (US). HOUGHTON, Raymond; 2636 - 242nd Place S.E., Bothell, WA 98021 (US). VEDVICK, Thomas, H.; 1301 Spring Street, Seattle, WA 98104 (US). TWARDZIK, Daniel, R.; 10195 South Beach Drive, Bainbridge Island, WA 98110 (US).			

(54) Title: COMPOUNDS AND METHODS FOR IMMUNOTHERAPY AND DIAGNOSIS OF TUBERCULOSIS

(57) Abstract

Compounds and methods for inducing protective immunity against tuberculosis are disclosed. The compounds provided include polypeptides that contain at least one immunogenic portion of one or more *M. tuberculosis* proteins and DNA molecules encoding such polypeptides. Such compounds may be formulated into vaccines and/or pharmaceutical compositions for immunization against *M. tuberculosis* infection, or may be used for the diagnosis of tuberculosis.



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Description5                   COMPOUNDS AND METHODS FOR IMMUNOTHERAPY  
AND DIAGNOSIS OF TUBERCULOSISTechnical Field

10                   The present invention relates generally to detecting, treating and preventing *Mycobacterium tuberculosis* infection. The invention is more particularly related to polypeptides comprising a *Mycobacterium tuberculosis* antigen, or a portion or other variant thereof, and the use of such polypeptides for diagnosing and vaccinating against *Mycobacterium tuberculosis* infection.

15

Background of the Invention

Tuberculosis is a chronic, infectious disease, that is generally caused by infection with *Mycobacterium tuberculosis*. It is a major disease in developing countries, as well as an increasing problem in developed areas of the world, with about  
20   8 million new cases and 3 million deaths each year. Although the infection may be asymptomatic for a considerable period of time, the disease is most commonly manifested as an acute inflammation of the lungs, resulting in fever and a nonproductive cough. If left untreated, serious complications and death typically result.

Although tuberculosis can generally be controlled using extended  
25   antibiotic therapy, such treatment is not sufficient to prevent the spread of the disease. Infected individuals may be asymptomatic, but contagious, for some time. In addition,

although compliance with the treatment regimen is critical, patient behavior is difficult to monitor. Some patients do not complete the course of treatment, which can lead to ineffective treatment and the development of drug resistance.

Inhibiting the spread of tuberculosis requires effective vaccination and accurate, early diagnosis of the disease. Currently, vaccination with live bacteria is the most efficient method for inducing protective immunity. The most common *Mycobacterium* employed for this purpose is *Bacillus Calmette-Guerin* (BCG), an avirulent strain of *Mycobacterium bovis*. However, the safety and efficacy of BCG is a source of controversy and some countries, such as the United States, do not vaccinate the general public. Diagnosis is commonly achieved using a skin test, which involves intradermal exposure to tuberculin PPD (protein-purified derivative). Antigen-specific T cell responses result in measurable induration at the injection site by 48-72 hours after injection, which indicates exposure to Mycobacterial antigens. Sensitivity and specificity have, however, been a problem with this test, and individuals vaccinated with BCG cannot be distinguished from infected individuals.

While macrophages have been shown to act as the principal effectors of *M. tuberculosis* immunity, T cells are the predominant inducers of such immunity. The essential role of T cells in protection against *M. tuberculosis* infection is illustrated by the frequent occurrence of *M. tuberculosis* in AIDS patients, due to the depletion of CD4 T cells associated with human immunodeficiency virus (HIV) infection. Mycobacterium-reactive CD4 T cells have been shown to be potent producers of gamma-interferon (IFN- $\gamma$ ), which, in turn, has been shown to trigger the anti-mycobacterial effects of macrophages in mice. While the role of IFN- $\gamma$  in humans is less clear, studies have shown that 1,25-dihydroxy-vitamin D3, either alone or in combination with IFN- $\gamma$  or tumor necrosis factor-alpha, activates human macrophages to inhibit *M. tuberculosis* infection. Furthermore, it is known that IFN- $\gamma$  stimulates human macrophages to make 1,25-dihydroxy-vitamin D3. Similarly, IL-12 has been shown to play a role in stimulating resistance to *M. tuberculosis* infection. For a review of the immunology of *M. tuberculosis* infection see Chan and Kaufmann in

*Tuberculosis: Pathogenesis, Protection and Control*, Bloom (ed.), ASM Press, Washington, DC, 1994.

Accordingly, there is a need in the art for improved vaccines and methods for preventing, treating and detecting tuberculosis. The present invention fulfills these needs and further provides other related advantages.

#### Summary of the Invention

Briefly stated, this invention provides compounds and methods for preventing and diagnosing tuberculosis. In one aspect, polypeptides are provided comprising an immunogenic portion of a soluble *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications. In one embodiment of this aspect, the soluble antigen has one of the following N-terminal sequences:

- (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Cys-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu; (SEQ ID No. 120)
- (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser; (SEQ ID No. 121)
- (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg; (SEQ ID No. 122)
- (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro; (SEQ ID No. 123)
- (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val; (SEQ ID No. 124)
- (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro; (SEQ ID No. 125)
- (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Thr-Ala-Ala-Ser-Pro-Pro-Ser; (SEQ ID No. 126)
- (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-Gly; (SEQ ID No. 127)

- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Leu-Thr-Ser-Leu-Leu-Asn-Ser-Leu-Ala-Asp-Pro-Asn-Val-Ser-Phe-Ala-Asn; (SEQ ID No. 128)
- (j) Xaa-Asp-Ser-Glu-Lys-Ser-Ala-Thr-Ile-Lys-Val-Thr-Asp-Ala-Ser; (SEQ ID No. 134)
- (k) Ala-Gly-Asp-Thr-Xaa-Ile-Tyr-Ile-Val-Gly-Asn-Leu-Thr-Ala-Asp; (SEQ ID No. 135) or
- (l) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 136)

10 wherein Xaa may be any amino acid.

In a related aspect, polypeptides are provided comprising an immunogenic portion of an *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications, the antigen having one of the following N-terminal sequences:

- (m) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No. 137) or
- (n) Asp-Pro-Pro-Asp-Pro-His-Gln-Xaa-Asp-Met-Thr-Lys-Gly-Tyr-Tyr-Pro-Gly-Gly-Arg-Arg-Xaa-Phe; (SEQ ID No. 129)

wherein Xaa may be any amino acid.

20 In another embodiment, the antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos.: 1, 2, 4-10, 13-25, 52, 99 and 101, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 1, 2, 4-10, 13-25, 52, 99 and 101 or a complement thereof under moderately stringent  
25 conditions.

In a related aspect, the polypeptides comprise an immunogenic portion of a *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications, wherein the antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of  
30 the sequences recited in SEQ ID Nos.: 26-51, the complements of said sequences, and

DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 26-51 or a complement thereof under moderately stringent conditions.

In related aspects, DNA sequences encoding the above polypeptides, expression vectors comprising these DNA sequences and host cells transformed or transfected with such expression vectors are also provided.

In another aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, an inventive polypeptide and a known *M. tuberculosis* antigen.

Within other aspects, the present invention provides pharmaceutical compositions that comprise one or more of the above polypeptides, or a DNA molecule encoding such polypeptides, and a physiologically acceptable carrier. The invention also provides vaccines comprising one or more of the polypeptides as described above and a non-specific immune response enhancer, together with vaccines comprising one or more DNA sequences encoding such polypeptides and a non-specific immune response enhancer.

In yet another aspect, methods are provided for inducing protective immunity in a patient, comprising administering to a patient an effective amount of one or more of the above polypeptides.

In further aspects of this invention, methods and diagnostic kits are provided for detecting tuberculosis in a patient. The methods comprise contacting dermal cells of a patient with one or more of the above polypeptides and detecting an immune response on the patient's skin. The diagnostic kits comprise one or more of the above polypeptides in combination with an apparatus sufficient to contact the polypeptide with the dermal cells of a patient.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

Brief Description of the Drawings and Sequence Identifiers

Figure 1A and B illustrate the stimulation of proliferation and interferon- $\gamma$  production in T cells derived from a first and a second *M. tuberculosis*-immune donor, respectively, by the 14 Kd, 20 Kd and 26 Kd antigens described in Example 1.

5           Figure 2 illustrates the stimulation of proliferation and interferon- $\gamma$  production in T cells derived from an *M. tuberculosis*-immune individual by the two representative polypeptides TbRa3 and TbRa9.

SEQ. ID NO. 1 is the DNA sequence of TbRa1.  
10       SEQ. ID NO. 2 is the DNA sequence of TbRa10.  
SEQ. ID NO. 3 is the DNA sequence of TbRa11.  
SEQ. ID NO. 4 is the DNA sequence of TbRa12.  
SEQ. ID NO. 5 is the DNA sequence of TbRa13.  
SEQ. ID NO. 6 is the DNA sequence of TbRa16.  
15       SEQ. ID NO. 7 is the DNA sequence of TbRa17.  
SEQ. ID NO. 8 is the DNA sequence of TbRa18.  
SEQ. ID NO. 9 is the DNA sequence of TbRa19.  
SEQ. ID NO. 10 is the DNA sequence of TbRa24.  
SEQ. ID NO. 11 is the DNA sequence of TbRa26.  
20       SEQ. ID NO. 12 is the DNA sequence of TbRa28.  
SEQ. ID NO. 13 is the DNA sequence of TbRa29.  
SEQ. ID NO. 14 is the DNA sequence of TbRa2A.  
SEQ. ID NO. 15 is the DNA sequence of TbRa3.  
SEQ. ID NO. 16 is the DNA sequence of TbRa32.  
25       SEQ. ID NO. 17 is the DNA sequence of TbRa35.  
SEQ. ID NO. 18 is the DNA sequence of TbRa36.  
SEQ. ID NO. 19 is the DNA sequence of TbRa4.  
SEQ. ID NO. 20 is the DNA sequence of TbRa9.  
SEQ. ID NO. 21 is the DNA sequence of TbRaB.  
30       SEQ. ID NO. 22 is the DNA sequence of TbRaC.

- SEQ. ID NO. 23 is the DNA sequence of TbRaD.  
SEQ. ID NO. 24 is the DNA sequence of YYWCPG.  
SEQ. ID NO. 25 is the DNA sequence of AAMK.  
SEQ. ID NO. 26 is the DNA sequence of TbL-23.  
5 SEQ. ID NO. 27 is the DNA sequence of TbL-24.  
SEQ. ID NO. 28 is the DNA sequence of TbL-25.  
SEQ. ID NO. 29 is the DNA sequence of TbL-28.  
SEQ. ID NO. 30 is the DNA sequence of TbL-29.  
SEQ. ID NO. 31 is the DNA sequence of TbH-5.  
10 SEQ. ID NO. 32 is the DNA sequence of TbH-8.  
SEQ. ID NO. 33 is the DNA sequence of TbH-9.  
SEQ. ID NO. 34 is the DNA sequence of TbM-1.  
SEQ. ID NO. 35 is the DNA sequence of TbM-3.  
SEQ. ID NO. 36 is the DNA sequence of TbM-6.  
15 SEQ. ID NO. 37 is the DNA sequence of TbM-7.  
SEQ. ID NO. 38 is the DNA sequence of TbM-9.  
SEQ. ID NO. 39 is the DNA sequence of TbM-12.  
SEQ. ID NO. 40 is the DNA sequence of TbM-13.  
SEQ. ID NO. 41 is the DNA sequence of TbM-14.  
20 SEQ. ID NO. 42 is the DNA sequence of TbM-15.  
SEQ. ID NO. 43 is the DNA sequence of TbH-4.  
SEQ. ID NO. 44 is the DNA sequence of TbH-4-FWD.  
SEQ. ID NO. 45 is the DNA sequence of TbH-12.  
SEQ. ID NO. 46 is the DNA sequence of Tb38-1.  
25 SEQ. ID NO. 47 is the DNA sequence of Tb38-4.  
SEQ. ID NO. 48 is the DNA sequence of TbL-17.  
SEQ. ID NO. 49 is the DNA sequence of TbL-20.  
SEQ. ID NO. 50 is the DNA sequence of TbL-21.  
SEQ. ID NO. 51 is the DNA sequence of TbH-16.  
30 SEQ. ID NO. 52 is the DNA sequence of DPEP.

- SEQ. ID NO. 53 is the deduced amino acid sequence of DPEP.
- SEQ. ID NO. 54 is the protein sequence of DPV N-terminal Antigen.
- SEQ. ID NO. 55 is the protein sequence of AVGS N-terminal Antigen.
- SEQ. ID NO. 56 is the protein sequence of AAMK N-terminal Antigen.
- 5 SEQ. ID NO. 57 is the protein sequence of YYWC N-terminal Antigen.
- SEQ. ID NO. 58 is the protein sequence of DIGS N-terminal Antigen.
- SEQ. ID NO. 59 is the protein sequence of AEES N-terminal Antigen.
- SEQ. ID NO. 60 is the protein sequence of DPEP N-terminal Antigen.
- SEQ. ID NO. 61 is the protein sequence of APKT N-terminal Antigen.
- 10 SEQ. ID NO. 62 is the protein sequence of DPAS N-terminal Antigen.
- SEQ. ID NO. 63 is the deduced amino acid sequence of TbRa1.
- SEQ. ID NO. 64 is the deduced amino acid sequence of TbRa10.
- SEQ. ID NO. 65 is the deduced amino acid sequence of TbRa11.
- SEQ. ID NO. 66 is the deduced amino acid sequence of TbRa12.
- 15 SEQ. ID NO. 67 is the deduced amino acid sequence of TbRa13.
- SEQ. ID NO. 68 is the deduced amino acid sequence of TbRa16.
- SEQ. ID NO. 69 is the deduced amino acid sequence of TbRa17.
- SEQ. ID NO. 70 is the deduced amino acid sequence of TbRa18.
- SEQ. ID NO. 71 is the deduced amino acid sequence of TbRa19.
- 20 SEQ. ID NO. 72 is the deduced amino acid sequence of TbRa24.
- SEQ. ID NO. 73 is the deduced amino acid sequence of TbRa26.
- SEQ. ID NO. 74 is the deduced amino acid sequence of TbRa28.
- SEQ. ID NO. 75 is the deduced amino acid sequence of TbRa29.
- SEQ. ID NO. 76 is the deduced amino acid sequence of TbRa2A.
- 25 SEQ. ID NO. 77 is the deduced amino acid sequence of TbRa3.
- SEQ. ID NO. 78 is the deduced amino acid sequence of TbRa32.
- SEQ. ID NO. 79 is the deduced amino acid sequence of TbRa35.
- SEQ. ID NO. 80 is the deduced amino acid sequence of TbRa36.
- SEQ. ID NO. 81 is the deduced amino acid sequence of TbRa4.
- 30 SEQ. ID NO. 82 is the deduced amino acid sequence of TbRa9.

- SEQ. ID NO. 83 is the deduced amino acid sequence of TbRaB.  
SEQ. ID NO. 84 is the deduced amino acid sequence of TbRaC.  
SEQ. ID NO. 85 is the deduced amino acid sequence of TbRaD.  
SEQ. ID NO. 86 is the deduced amino acid sequence of YYWCPG.  
5 SEQ. ID NO. 87 is the deduced amino acid sequence of TbAAMK.  
SEQ. ID NO. 88 is the deduced amino acid sequence of Tb38-1.  
SEQ. ID NO. 89 is the deduced amino acid sequence of TbH-4.  
SEQ. ID NO. 90 is the deduced amino acid sequence of TbH-8.  
SEQ. ID NO. 91 is the deduced amino acid sequence of TbH-9.  
10 SEQ. ID NO. 92 is the deduced amino acid sequence of TbH-12.  
SEQ. ID NO. 93 is the amino acid sequence of Tb38-1 Peptide 1.  
SEQ. ID NO. 94 is the amino acid sequence of Tb38-1 Peptide 2.  
SEQ. ID NO. 95 is the amino acid sequence of Tb38-1 Peptide 3.  
SEQ. ID NO. 96 is the amino acid sequence of Tb38-1 Peptide 4.  
15 SEQ. ID NO. 97 is the amino acid sequence of Tb38-1 Peptide 5.  
SEQ. ID NO. 98 is the amino acid sequence of Tb38-1 Peptide 6.  
SEQ. ID NO. 99 is the DNA sequence of DPAS.  
SEQ. ID NO. 100 is the deduced amino acid sequence of DPAS.  
SEQ. ID NO. 101 is the DNA sequence of DPV.  
20 SEQ. ID NO. 102 is the deduced amino acid sequence of DPV.  
SEQ. ID NO. 103 is the DNA sequence of ESAT-6.  
SEQ. ID NO. 104 is the deduced amino acid sequence of ESAT-6.  
SEQ. ID NO. 105 is the DNA sequence of TbH-8-2.  
SEQ. ID NO. 106 is the DNA sequence of TbH-9FL.  
25 SEQ. ID NO. 107 is the deduced amino acid sequence of TbH-9FL.  
SEQ. ID NO. 108 is the DNA sequence of TbH-9-1.  
SEQ. ID NO. 109 is the deduced amino acid sequence of TbH-9-1.  
SEQ. ID NO. 110 is the DNA sequence of TbH-9-4.  
SEQ. ID NO. 111 is the deduced amino acid sequence of TbH-9-4.  
30 SEQ. ID NO. 112 is the DNA sequence of Tb38-1F2 IN.

- SEQ. ID NO. 113 is the DNA sequence of Tb38-2F2 RP.
- SEQ. ID NO. 114 is the deduced amino acid sequence of Tb37-FL.
- SEQ. ID NO. 115 is the deduced amino acid sequence of Tb38-IN.
- SEQ. ID NO. 116 is the DNA sequence of Tb38-1F3.
- 5 SEQ. ID NO. 117 is the deduced amino acid sequence of Tb38-1F3.
- SEQ. ID NO. 118 is the DNA sequence of Tb38-1F5.
- SEQ. ID NO. 119 is the DNA sequence of Tb38-1F6.
- SEQ. ID NO. 120 is the deduced N-terminal amino acid sequence of DPV.
- SEQ. ID NO. 121 is the deduced N-terminal amino acid sequence of AVGS.
- 10 SEQ. ID NO. 122 is the deduced N-terminal amino acid sequence of AAMK.
- SEQ. ID NO. 123 is the deduced N-terminal amino acid sequence of YYWC.
- SEQ. ID NO. 124 is the deduced N-terminal amino acid sequence of DIGS.
- SEQ. ID NO. 125 is the deduced N-terminal amino acid sequence of AEES.
- SEQ. ID NO. 126 is the deduced N-terminal amino acid sequence of DPEP.
- 15 SEQ. ID NO. 127 is the deduced N-terminal amino acid sequence of APKT.
- SEQ. ID NO. 128 is the deduced amino acid sequence of DPAS.
- SEQ. ID NO. 129 is the protein sequence of DPPD N-terminal Antigen.
- SEQ ID NO. 130-133 are the protein sequences of four DPPD cyanogen bromide fragments.
- 20 SEQ ID NO. 134 is the N-terminal protein sequence of XDS antigen.
- SEQ ID NO. 135 is the N-terminal protein sequence of AGD antigen.
- SEQ ID NO. 136 is the N-terminal protein sequence of APE antigen.
- SEQ ID NO. 137 is the N-terminal protein sequence of XYI antigen.

## 25 Detailed Description of the Invention

As noted above, the present invention is generally directed to compositions and methods for preventing, treating and diagnosing tuberculosis. The compositions of the subject invention include polypeptides that comprise at least one immunogenic portion of a *M. tuberculosis* antigen, or a variant of such an antigen that

30 differs only in conservative substitutions and/or modifications. Polypeptides within the scope of the present invention include, but are not limited to, immunogenic soluble

*M. tuberculosis* antigens. A "soluble *M. tuberculosis* antigen" is a protein of *M. tuberculosis* origin that is present in *M. tuberculosis* culture filtrate. As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full length proteins (*i.e.*, antigens), wherein the amino acid residues are linked by covalent peptide bonds. Thus, a polypeptide comprising an immunogenic portion of one of the above antigens may consist entirely of the immunogenic portion, or may contain additional sequences. The additional sequences may be derived from the native *M. tuberculosis* antigen or may be heterologous, and such sequences may (but need not) be immunogenic.

"Immunogenic," as used herein, refers to the ability to elicit an immune response (*e.g.*, cellular) in a patient, such as a human, and/or in a biological sample. In particular, antigens that are immunogenic (and immunogenic portions or other variants of such antigens) are capable of stimulating cell proliferation, interleukin-12 production and/or interferon- $\gamma$  production in biological samples comprising one or more cells selected from the group of T cells, NK cells, B cells and macrophages, where the cells are derived from an *M. tuberculosis*-immune individual. Polypeptides comprising at least an immunogenic portion of one or more *M. tuberculosis* antigens may generally be used to detect tuberculosis or to induce protective immunity against tuberculosis in a patient.

The compositions and methods of this invention also encompass variants of the above polypeptides. A "variant," as used herein, is a polypeptide that differs from the native antigen only in conservative substitutions and/or modifications, such that the ability of the polypeptide to induce an immune response is retained. Such variants may generally be identified by modifying one of the above polypeptide sequences, and evaluating the immunogenic properties of the modified polypeptide using, for example, the representative procedures described herein.

A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydrophobic nature of the polypeptide to be substantially unchanged. In general, the following

groups of amino acids represent conservative changes: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

5 Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenic properties, secondary structure and hydrophobic nature of the polypeptide. For example, a polypeptide may be conjugated to a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease  
10 of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

In a related aspect, combination polypeptides are disclosed. A "combination polypeptide" is a polypeptide comprising at least one of the above  
15 immunogenic portions and one or more additional immunogenic *M. tuberculosis* sequences, which are joined via a peptide linkage into a single amino acid chain. The sequences may be joined directly (*i.e.*, with no intervening amino acids) or may be joined by way of a linker sequence (*e.g.*, Gly-Cys-Gly) that does not significantly diminish the immunogenic properties of the component polypeptides.

20 In general, *M. tuberculosis* antigens, and DNA sequences encoding such antigens, may be prepared using any of a variety of procedures. For example, soluble antigens may be isolated from *M. tuberculosis* culture filtrate by procedures known to those of ordinary skill in the art, including anion-exchange and reverse phase chromatography. Purified antigens are then evaluated for their ability to elicit an  
25 appropriate immune response (*e.g.*, cellular) using, for example, the representative methods described herein. Immunogenic antigens may then be partially sequenced using techniques such as traditional Edman chemistry. *See* Edman and Berg, *Eur. J. Biochem.* 80:116-132, 1967.

Immunogenic antigens may also be produced recombinantly using a  
30 DNA sequence that encodes the antigen, which has been inserted into an expression

vector and expressed in an appropriate host. DNA molecules encoding soluble antigens may be isolated by screening an appropriate *M. tuberculosis* expression library with anti-sera (*e.g.*, rabbit) raised specifically against soluble *M. tuberculosis* antigens. DNA sequences encoding antigens that may or may not be soluble may be identified by  
5 screening an appropriate *M. tuberculosis* genomic or cDNA expression library with sera obtained from patients infected with *M. tuberculosis*. Such screens may generally be performed using techniques well known to those of ordinary skill in the art, such as those described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989.

10 DNA sequences encoding soluble antigens may also be obtained by screening an appropriate *M. tuberculosis* cDNA or genomic DNA library for DNA sequences that hybridize to degenerate oligonucleotides derived from partial amino acid sequences of isolated soluble antigens. Degenerate oligonucleotide sequences for use in such a screen may be designed and synthesized, and the screen may be performed, as  
15 described (for example) in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989 (and references cited therein). Polymerase chain reaction (PCR) may also be employed, using the above oligonucleotides in methods well known in the art, to isolate a nucleic acid probe from a cDNA or genomic library. The library screen may then be performed using the isolated  
20 probe.

Alternatively, genomic or cDNA libraries derived from *M. tuberculosis* may be screened directly using peripheral blood mononuclear cells (PBMCs) or T cell lines or clones derived from one or more *M. tuberculosis*-immune individuals. In general, PBMCs and/or T cells for use in such screens may be prepared as described  
25 below. Direct library screens may generally be performed by assaying pools of expressed recombinant proteins for the ability to induce proliferation and/or interferon- $\gamma$  production in T cells derived from an *M. tuberculosis*-immune individual. Alternatively, potential T cell antigens may be first selected based on antibody reactivity, as described above.

Regardless of the method of preparation, the antigens (and immunogenic portions thereof) described herein (which may or may not be soluble) have the ability to induce an immunogenic response. More specifically, the antigens have the ability to induce proliferation and/or cytokine production (*i.e.*, interferon- $\gamma$  and/or interleukin-12 production) in T cells, NK cells, B cells and/or macrophages derived from an *M. tuberculosis*-immune individual. The selection of cell type for use in evaluating an immunogenic response to a antigen will, of course, depend on the desired response. For example, interleukin-12 production is most readily evaluated using preparations containing B cells and/or macrophages. An *M. tuberculosis*-immune individual is one who is considered to be resistant to the development of tuberculosis by virtue of having mounted an effective T cell response to *M. tuberculosis* (*i.e.*, substantially free of disease symptoms). Such individuals may be identified based on a strongly positive (*i.e.*, greater than about 10 mm diameter induration) intradermal skin test response to tuberculosis proteins (PPD) and an absence of any signs or symptoms of tuberculosis disease. T cells, NK cells, B cells and macrophages derived from *M. tuberculosis*-immune individuals may be prepared using methods known to those of ordinary skill in the art. For example, a preparation of PBMCs (*i.e.*, peripheral blood mononuclear cells) may be employed without further separation of component cells. PBMCs may generally be prepared, for example, using density centrifugation through Ficoll™ (Winthrop Laboratories, NY). T cells for use in the assays described herein may also be purified directly from PBMCs. Alternatively, an enriched T cell line reactive against mycobacterial proteins, or T cell clones reactive to individual mycobacterial proteins, may be employed. Such T cell clones may be generated by, for example, culturing PBMCs from *M. tuberculosis*-immune individuals with mycobacterial proteins for a period of 2-4 weeks. This allows expansion of only the mycobacterial protein-specific T cells, resulting in a line composed solely of such cells. These cells may then be cloned and tested with individual proteins, using methods known to those of ordinary skill in the art, to more accurately define individual T cell specificity. In general, antigens that test positive in assays for proliferation and/or cytokine production (*i.e.*, interferon- $\gamma$  and/or interleukin-12 production) performed using T cells, NK cells, B cells

and/or macrophages derived from an *M. tuberculosis*-immune individual are considered immunogenic. Such assays may be performed, for example, using the representative procedures described below. Immunogenic portions of such antigens may be identified using similar assays, and may be present within the polypeptides described herein.

5           The ability of a polypeptide (*e.g.*, an immunogenic antigen, or a portion or other variant thereof) to induce cell proliferation is evaluated by contacting the cells (*e.g.*, T cells and/or NK cells) with the polypeptide and measuring the proliferation of the cells. In general, the amount of polypeptide that is sufficient for evaluation of about  $10^5$  cells ranges from about 10 ng/mL to about 100  $\mu$ g/mL and preferably is about  
10   10  $\mu$ g/mL. The incubation of polypeptide with cells is typically performed at 37°C for about six days. Following incubation with polypeptide, the cells are assayed for a proliferative response, which may be evaluated by methods known to those of ordinary skill in the art, such as exposing cells to a pulse of radiolabeled thymidine and measuring the incorporation of label into cellular DNA. In general, a polypeptide that  
15   results in at least a three fold increase in proliferation above background (*i.e.*, the proliferation observed for cells cultured without polypeptide) is considered to be able to induce proliferation.

          The ability of a polypeptide to stimulate the production of interferon- $\gamma$  and/or interleukin-12 in cells may be evaluated by contacting the cells with the  
20   polypeptide and measuring the level of interferon- $\gamma$  or interleukin-12 produced by the cells. In general, the amount of polypeptide that is sufficient for the evaluation of about  $10^5$  cells ranges from about 10 ng/mL to about 100  $\mu$ g/mL and preferably is about 10  $\mu$ g/mL. The polypeptide may, but need not, be immobilized on a solid support, such as a bead or a biodegradable microsphere, such as those described in U.S. Patent  
25   Nos. 4,897,268 and 5,075,109. The incubation of polypeptide with the cells is typically performed at 37°C for about six days. Following incubation with polypeptide, the cells are assayed for interferon- $\gamma$  and/or interleukin-12 (or one or more subunits thereof), which may be evaluated by methods known to those of ordinary skill in the art, such as an enzyme-linked immunosorbent assay (ELISA) or, in the case of IL-12 P70 subunit, a  
30   bioassay such as an assay measuring proliferation of T cells. In general, a polypeptide

that results in the production of at least 50 pg of interferon- $\gamma$  per mL of cultured supernatant (containing  $10^4$ - $10^5$  T cells per mL) is considered able to stimulate the production of interferon- $\gamma$ . A polypeptide that stimulates the production of at least 10 pg/mL of IL-12 P70 subunit, and/or at least 100 pg/mL of IL-12 P40 subunit, per  $10^5$  macrophages or B cells (or per  $3 \times 10^5$  PBMC) is considered able to stimulate the production of IL-12.

In general, immunogenic antigens are those antigens that stimulate proliferation and/or cytokine production (*i.e.*, interferon- $\gamma$  and/or interleukin-12 production) in T cells, NK cells, B cells and/or macrophages derived from at least about 25% of *M. tuberculosis*-immune individuals. Among these immunogenic antigens, polypeptides having superior therapeutic properties may be distinguished based on the magnitude of the responses in the above assays and based on the percentage of individuals for which a response is observed. In addition, antigens having superior therapeutic properties will not stimulate proliferation and/or cytokine production *in vitro* in cells derived from more than about 25% of individuals that are not *M. tuberculosis*-immune, thereby eliminating responses that are not specifically due to *M. tuberculosis*-responsive cells. Those antigens that induce a response in a high percentage of T cell, NK cell, B cell and/or macrophage preparations from *M. tuberculosis*-immune individuals (with a low incidence of responses in cell preparations from other individuals) have superior therapeutic properties.

Antigens with superior therapeutic properties may also be identified based on their ability to diminish the severity of *M. tuberculosis* infection in experimental animals, when administered as a vaccine. Suitable vaccine preparations for use on experimental animals are described in detail below. Efficacy may be determined based on the ability of the antigen to provide at least about a 50% reduction in bacterial numbers and/or at least about a 40% decrease in mortality following experimental infection. Suitable experimental animals include mice, guinea pigs and primates.

Antigens having superior diagnostic properties may generally be identified based on the ability to elicit a response in an intradermal skin test performed

on an individual with active tuberculosis, but not in a test performed on an individual who is not infected with *M. tuberculosis*. Skin tests may generally be performed as described below, with a response of at least 5 mm induration considered positive.

Immunogenic portions of the antigens described herein may be prepared  
5 and identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3d ed., Raven Press, 1993, pp. 243-247 and references cited therein. Such techniques include screening polypeptide portions of the native antigen for immunogenic properties. The representative proliferation and cytokine production assays described herein may generally be employed in these screens. An immunogenic  
10 portion of a polypeptide is a portion that, within such representative assays, generates an immune response (e.g., proliferation, interferon- $\gamma$  production and/or interleukin-12 production) that is substantially similar to that generated by the full length antigen. In other words, an immunogenic portion of an antigen may generate at least about 20%, and preferably about 100%, of the proliferation induced by the full length antigen in the  
15 model proliferation assay described herein. An immunogenic portion may also, or alternatively, stimulate the production of at least about 20%, and preferably about 100%, of the interferon- $\gamma$  and/or interleukin-12 induced by the full length antigen in the model assay described herein.

Portions and other variants of *M. tuberculosis* antigens may be generated  
20 by synthetic or recombinant means. Synthetic polypeptides having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are  
25 sequentially added to a growing amino acid chain. See Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Applied BioSystems, Inc., Foster City, CA, and may be operated according to the manufacturer's instructions. Variants of a native antigen may generally be prepared using standard mutagenesis techniques, such  
30 as oligonucleotide-directed site-specific mutagenesis. Sections of the DNA sequence

may also be removed using standard techniques to permit preparation of truncated polypeptides.

Recombinant polypeptides containing portions and/or variants of a native antigen may be readily prepared from a DNA sequence encoding the polypeptide using a variety of techniques well known to those of ordinary skill in the art. For example, supernatants from suitable host/vector systems which secrete recombinant protein into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant protein.

Any of a variety of expression vectors known to those of ordinary skill in the art may be employed to express recombinant polypeptides of this invention. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. The DNA sequences expressed in this manner may encode naturally occurring antigens, portions of naturally occurring antigens, or other variants thereof.

In general, regardless of the method of preparation, the polypeptides disclosed herein are prepared in substantially pure form. Preferably, the polypeptides are at least about 80% pure, more preferably at least about 90% pure and most preferably at least about 99% pure. In certain preferred embodiments, described in detail below, the substantially pure polypeptides are incorporated into pharmaceutical compositions or vaccines for use in one or more of the methods disclosed herein.

In certain specific embodiments, the subject invention discloses polypeptides comprising at least an immunogenic portion of a soluble *M. tuberculosis* antigen having one of the following N-terminal sequences, or a variant thereof that differs only in conservative substitutions and/or modifications:

- 5 (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Cys-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu; (SEQ ID No. 120)
- (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser; (SEQ ID No. 121)
- 10 (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg; (SEQ ID No. 122)
- (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro; (SEQ ID No. 123)
- (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val; (SEQ ID No. 124)
- 15 (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro; (SEQ ID No. 125)
- (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Ala-Ala-Ala-Ser-Pro-Pro-Ser; (SEQ ID No. 126)
- 20 (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-Gly; (SEQ ID No. 127)
- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Leu-Thr-Ser-Leu-Leu-Asn-Ser-Leu-Ala-Asp-Pro-Asn-Val-Ser-Phe-Ala-Asn; (SEQ ID No. 128)
- 25 (j) Xaa-Asp-Ser-Glu-Lys-Ser-Ala-Thr-Ile-Lys-Val-Thr-Asp-Ala-Ser; (SEQ ID No. 134)
- (k) Ala-Gly-Asp-Thr-Xaa-Ile-Tyr-Ile-Val-Gly-Asn-Leu-Thr-Ala-Asp; (SEQ ID No. 135) or
- (l) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 136)

wherein Xaa may be any amino acid, preferably a cysteine residue. A DNA sequence encoding the antigen identified as (g) above is provided in SEQ ID No. 52, and the polypeptide encoded by SEQ ID No. 52 is provided in SEQ ID No. 53. A DNA sequence encoding the antigen defined as (a) above is provided in SEQ ID No. 101; its deduced amino acid sequence is provided in SEQ ID No. 102. A DNA sequence

corresponding to antigen (d) above is provided in SEQ ID No. 24 a DNA sequence corresponding to antigen (c) is provided in SEQ ID No. 25 and a DNA sequence corresponding to antigen (i) is provided in SEQ ID No. 99; its deduced amino acid sequence is provided in SEQ ID No. 100.

5 In a further specific embodiment, the subject invention discloses polypeptides comprising at least an immunogenic portion of an *M. tuberculosis* antigen having one of the following N-terminal sequences, or a variant thereof that differs only in conservative substitutions and/or modifications:

- 10 (m) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No 137) or
- (n) Asp-Pro-Pro-Asp-Pro-His-Gln-Xaa-Asp-Met-Thr-Lys-Gly-Tyr-Tyr-Pro-Gly-Gly-Arg-Arg-Xaa-Phe; (SEQ ID No. 129)

wherein Xaa may be any amino acid, preferably a cysteine residue.

15 In other specific embodiments, the subject invention discloses polypeptides comprising at least an immunogenic portion of a soluble *M. tuberculosis* antigen (or a variant of such an antigen) that comprises one or more of the amino acid sequences encoded by (a) the DNA sequences of SEQ ID Nos.: 1, 2, 4-10, 13-25 and 52; (b) the complements of such DNA sequences, or (c) DNA sequences substantially homologous to a sequence in (a) or (b).

20 In further specific embodiments, the subject invention discloses polypeptides comprising at least an immunogenic portion of a *M. tuberculosis* antigen (or a variant of such an antigen), which may or may not be soluble, that comprises one or more of the amino acid sequences encoded by (a) the DNA sequences of SEQ ID Nos.: 26-51, (b) the complements of such DNA sequences or (c) DNA sequences

25 substantially homologous to a sequence in (a) or (b).

In the specific embodiments discussed above, the *M. tuberculosis* antigens include variants that are encoded by DNA sequences which are substantially homologous to one or more of DNA sequences specifically recited herein. "Substantial homology," as used herein, refers to DNA sequences that are capable of hybridizing

30 under moderately stringent conditions. Suitable moderately stringent conditions include

prewashing in a solution of 5X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5X SSC, overnight or, in the case of cross-species homology at 45°C, 0.5X SSC; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS). Such hybridizing DNA sequences are also  
5 within the scope of this invention, as are nucleotide sequences that, due to code degeneracy, encode an immunogenic polypeptide that is encoded by a hybridizing DNA sequence.

In a related aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, a polypeptide of  
10 the present invention and a known *M tuberculosis* antigen, such as the 38 kD antigen described above or ESAT-6 (SEQ ID Nos. 103 and 104), together with variants of such fusion proteins. The fusion proteins of the present invention may also include a linker peptide between the first and second polypeptides.

A DNA sequence encoding a fusion protein of the present invention is  
15 constructed using known recombinant DNA techniques to assemble separate DNA sequences encoding the first and second polypeptides into an appropriate expression vector. The 3' end of a DNA sequence encoding the first polypeptide is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide so that the reading frames of the sequences are in phase to permit mRNA  
20 translation of the two DNA sequences into a single fusion protein that retains the biological activity of both the first and the second polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptides by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into  
25 the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide  
30 functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser

residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene* 40:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent  
5 No. 4,751,180. The linker sequence may be from 1 to about 50 amino acids in length. Peptide sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable  
10 transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons require to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

15 In another aspect, the present invention provides methods for using one or more of the above polypeptides or fusion proteins (or DNA molecules encoding such polypeptides) to induce protective immunity against tuberculosis in a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may be afflicted with a disease, or may be free of detectable disease and/or infection. In  
20 other words, protective immunity may be induced to prevent or treat tuberculosis.

In this aspect, the polypeptide, fusion protein or DNA molecule is generally present within a pharmaceutical composition and/or a vaccine. Pharmaceutical compositions may comprise one or more polypeptides, each of which may contain one or more of the above sequences (or variants thereof), and a  
25 physiologically acceptable carrier. Vaccines may comprise one or more of the above polypeptides and a non-specific immune response enhancer, such as an adjuvant or a liposome (into which the polypeptide is incorporated). Such pharmaceutical compositions and vaccines may also contain other *M. tuberculosis* antigens, either incorporated into a combination polypeptide or present within a separate polypeptide.

Alternatively, a vaccine may contain DNA encoding one or more polypeptides as described above, such that the polypeptide is generated *in situ*. In such vaccines, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacterial and viral expression systems. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

In a related aspect, a DNA vaccine as described above may be administered simultaneously with or sequentially to either a polypeptide of the present invention or a known *M. tuberculosis* antigen, such as the 38 kD antigen described above. For example, administration of DNA encoding a polypeptide of the present invention, either "naked" or in a delivery system as described above, may be followed by administration of an antigen in order to enhance the protective immune effect of the vaccine.

Routes and frequency of administration, as well as dosage, will vary from individual to individual and may parallel those currently being used in immunization using BCG. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Between 1 and 3 doses may be administered for a 1-36 week period. Preferably, 3 doses are administered, at

intervals of 3-4 months, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of polypeptide or DNA that, when administered as described above, is capable of raising an immune response in an immunized patient sufficient to protect the patient from *M. tuberculosis* infection for at least 1-2 years. In general, the amount of polypeptide present in a dose (or produced *in situ* by the DNA in a dose) ranges from about 1 pg to about 100 mg per kg of host, typically from about 10 pg to about 1 mg, and preferably from about 100 pg to about 1  $\mu$ g. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactic galactide) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Any of a variety of adjuvants may be employed in the vaccines of this invention to nonspecifically enhance the immune response. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a nonspecific stimulator of immune responses, such as lipid A, *Bordetella pertussis* or *Mycobacterium tuberculosis*. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Freund's Complete Adjuvant (Difco Laboratories) and Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ). Other suitable adjuvants include alum, biodegradable microspheres, monophosphoryl lipid A and quil A.

In another aspect, this invention provides methods for using one or more of the polypeptides described above to diagnose tuberculosis using a skin test. As used

herein, a "skin test" is any assay performed directly on a patient in which a delayed-type hypersensitivity (DTH) reaction (such as swelling, reddening or dermatitis) is measured following intradermal injection of one or more polypeptides as described above. Such injection may be achieved using any suitable device sufficient to contact the  
5 polypeptide or polypeptides with dermal cells of the patient, such as a tuberculin syringe or 1 mL syringe. Preferably, the reaction is measured at least 48 hours after injection, more preferably 48-72 hours.

The DTH reaction is a cell-mediated immune response, which is greater in patients that have been exposed previously to the test antigen (*i.e.*, the immunogenic  
10 portion of the polypeptide employed, or a variant thereof). The response may be measured visually, using a ruler. In general, a response that is greater than about 0.5 cm in diameter, preferably greater than about 1.0 cm in diameter, is a positive response, indicative of tuberculosis infection, which may or may not be manifested as an active disease.

15 The polypeptides of this invention are preferably formulated, for use in a skin test, as pharmaceutical compositions containing a polypeptide and a physiologically acceptable carrier, as described above. Such compositions typically contain one or more of the above polypeptides in an amount ranging from about 1  $\mu$ g to about 100  $\mu$ g, preferably from about 10  $\mu$ g to about 50  $\mu$ g in a volume of 0.1 mL.  
20 Preferably, the carrier employed in such pharmaceutical compositions is a saline solution with appropriate preservatives, such as phenol and/or Tween 80™.

In a preferred embodiment, a polypeptide employed in a skin test is of sufficient size such that it remains at the site of injection for the duration of the reaction period. In general, a polypeptide that is at least 9 amino acids in length is sufficient.  
25 The polypeptide is also preferably broken down by macrophages within hours of injection to allow presentation to T-cells. Such polypeptides may contain repeats of one or more of the above sequences and/or other immunogenic or nonimmunogenic sequences.

The following Examples are offered by way of illustration and not by way of limitation.

## EXAMPLES

5

### EXAMPLE 1

#### PURIFICATION AND CHARACTERIZATION OF POLYPEPTIDES

##### FROM *M. TUBERCULOSIS* CULTURE FILTRATE

10 This example illustrates the preparation of *M. tuberculosis* soluble polypeptides from culture filtrate. Unless otherwise noted, all percentages in the following example are weight per volume.

*M. tuberculosis* (either H37Ra, ATCC No. 25177, or H37Rv, ATCC No. 25618) was cultured in sterile GAS media at 37°C for fourteen days. The media  
15 was then vacuum filtered (leaving the bulk of the cells) through a 0.45 µ filter into a sterile 2.5 L bottle. The media was next filtered through a 0.2 µ filter into a sterile 4 L bottle and NaN<sub>3</sub> was added to the culture filtrate to a concentration of 0.04%. The bottles were then placed in a 4°C cold room.

The culture filtrate was concentrated by placing the filtrate in a 12 L  
20 reservoir that had been autoclaved and feeding the filtrate into a 400 ml Amicon stir cell which had been rinsed with ethanol and contained a 10,000 kDa MWCO membrane. The pressure was maintained at 60 psi using nitrogen gas. This procedure reduced the 12 L volume to approximately 50 ml.

The culture filtrate was dialyzed into 0.1% ammonium bicarbonate using  
25 a 8,000 kDa MWCO cellulose ester membrane, with two changes of ammonium bicarbonate solution. Protein concentration was then determined by a commercially available BCA assay (Pierce, Rockford, IL).

The dialyzed culture filtrate was then lyophilized, and the polypeptides resuspended in distilled water. The polypeptides were dialyzed against 0.01 mM 1,3  
30 bis[tris(hydroxymethyl)-methylamino]propane, pH 7.5 (Bis-Tris propane buffer), the

initial conditions for anion exchange chromatography. Fractionation was performed using gel perfusion chromatography on a POROS 146 II Q/M anion exchange column 4.6 mm x 100 mm (Perseptive BioSystems, Framingham, MA) equilibrated in 0.01 mM Bis-Tris propane buffer pH 7.5. Polypeptides were eluted with a linear 0-0.5 M NaCl  
5 gradient in the above buffer system. The column eluent was monitored at a wavelength of 220 nm.

The pools of polypeptides eluting from the ion exchange column were dialyzed against distilled water and lyophilized. The resulting material was dissolved in 0.1% trifluoroacetic acid (TFA) pH 1.9 in water, and the polypeptides were purified on  
10 a Delta-Pak C18 column (Waters, Milford, MA) 300 Angstrom pore size, 5 micron particle size (3.9 x 150 mm). The polypeptides were eluted from the column with a linear gradient from 0-60% dilution buffer (0.1% TFA in acetonitrile). The flow rate was 0.75 ml/minute and the HPLC eluent was monitored at 214 nm. Fractions containing the eluted polypeptides were collected to maximize the purity of the  
15 individual samples. Approximately 200 purified polypeptides were obtained.

The purified polypeptides were then screened for the ability to induce T-cell proliferation in PBMC preparations. The PBMCs from donors known to be PPD skin test positive and whose T-cells were shown to proliferate in response to PPD and crude soluble proteins from MTB were cultured in medium comprising RPMI 1640  
20 supplemented with 10% pooled human serum and 50 µg/ml gentamicin. Purified polypeptides were added in duplicate at concentrations of 0.5 to 10 µg/mL. After six days of culture in 96-well round-bottom plates in a volume of 200 µl, 50 µl of medium was removed from each well for determination of IFN-γ levels, as described below. The plates were then pulsed with 1 µCi/well of tritiated thymidine for a further 18  
25 hours, harvested and tritium uptake determined using a gas scintillation counter. Fractions that resulted in proliferation in both replicates three fold greater than the proliferation observed in cells cultured in medium alone were considered positive.

IFN-γ was measured using an enzyme-linked immunosorbent assay (ELISA). ELISA plates were coated with a mouse monoclonal antibody directed to  
30 human IFN-γ (PharMingen, San Diego, CA) in PBS for four hours at room temperature.

Wells were then blocked with PBS containing 5% (W/V) non-fat dried milk for 1 hour at room temperature. The plates were then washed six times in PBS/0.2% TWEEN-20 and samples diluted 1:2 in culture medium in the ELISA plates were incubated overnight at room temperature. The plates were again washed and a polyclonal rabbit  
5 anti-human IFN- $\gamma$  serum diluted 1:3000 in PBS/10% normal goat serum was added to each well. The plates were then incubated for two hours at room temperature, washed and horseradish peroxidase-coupled anti-rabbit IgG (Sigma Chemical So., St. Louis, MO) was added at a 1:2000 dilution in PBS/5% non-fat dried milk. After a further two hour incubation at room temperature, the plates were washed and TMB substrate added.  
10 The reaction was stopped after 20 min with 1 N sulfuric acid. Optical density was determined at 450 nm using 570 nm as a reference wavelength. Fractions that resulted in both replicates giving an OD two fold greater than the mean OD from cells cultured in medium alone, plus 3 standard deviations, were considered positive.

For sequencing, the polypeptides were individually dried onto  
15 Biobrene™ (Perkin Elmer/Applied BioSystems Division, Foster City, CA) treated glass fiber filters. The filters with polypeptide were loaded onto a Perkin Elmer/Applied BioSystems Division Procise 492 protein sequencer. The polypeptides were sequenced from the amino terminal and using traditional Edman chemistry. The amino acid sequence was determined for each polypeptide by comparing the retention time of the  
20 PTH amino acid derivative to the appropriate PTH derivative standards.

Using the procedure described above, antigens having the following N-terminal sequences were isolated:

- (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Xaa-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu; (SEQ ID No. 54)
- 25 (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser; (SEQ ID No. 55)
- (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg; (SEQ ID No. 56)
- (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro; (SEQ ID No. 57)
- 30

- (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val;  
(SEQ ID No. 58)
- (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro; (SEQ ID  
No. 59)
- 5 (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Ala-Ala-Ala-Ala-  
Pro-Pro-Ala; (SEQ ID No. 60) and
- (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-  
Gly; (SEQ ID No. 61)

wherein Xaa may be any amino acid.

10 An additional antigen was isolated employing a microbore HPLC  
purification step in addition to the procedure described above. Specifically, 20  $\mu$ l of a  
fraction comprising a mixture of antigens from the chromatographic purification step  
previously described, was purified on an Aquapore C18 column (Perkin Elmer/Applied  
Biosystems Division, Foster City, CA) with a 7 micron pore size, column size 1 mm x  
15 100 mm, in a Perkin Elmer/Applied Biosystems Division Model 172 HPLC. Fractions  
were eluted from the column with a linear gradient of 1%/minute of acetonitrile  
(containing 0.05% TFA) in water (0.05% TFA) at a flow rate of 80  $\mu$ l/minute. The  
eluent was monitored at 250 nm. The original fraction was separated into 4 major peaks  
plus other smaller components and a polypeptide was obtained which was shown to  
20 have a molecular weight of 12.054 Kd (by mass spectrometry) and the following N-  
terminal sequence:

- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Gln-  
Thr-Ser-Leu-Leu-Asn-Asn-Leu-Ala-Asp-Pro-Asp-Val-Ser-Phe-  
Ala-Asp (SEQ ID No. 62).

25 This polypeptide was shown to induce proliferation and IFN- $\gamma$  production in PBMC  
preparations using the assays described above.

Additional soluble antigens were isolated from *M. tuberculosis* culture  
filtrate as follows. *M. tuberculosis* culture filtrate was prepared as described above.  
Following dialysis against Bis-Tris propane buffer, at pH 5.5, fractionation was  
30 performed using anion exchange chromatography on a Poros QE column 4.6 x 100 mm

(Perseptive Biosystems) equilibrated in Bis-Tris propane buffer pH 5.5. Polypeptides were eluted with a linear 0-1.5 M NaCl gradient in the above buffer system at a flow rate of 10 ml/min. The column eluent was monitored at a wavelength of 214 nm.

The fractions eluting from the ion exchange column were pooled and  
5 subjected to reverse phase chromatography using a Poros R2 column 4.6 x 100 mm (Perseptive Biosystems). Polypeptides were eluted from the column with a linear gradient from 0-100% acetonitrile (0.1% TFA) at a flow rate of 5 ml/min. The eluent was monitored at 214 nm.

Fractions containing the eluted polypeptides were lyophilized and  
10 resuspended in 80 µl of aqueous 0.1% TFA and further subjected to reverse phase chromatography on a Vydac C4 column 4.6 x 150 mm (Western Analytical, Temecula, CA) with a linear gradient of 0-100% acetonitrile (0.1% TFA) at a flow rate of 2 ml/min. Eluent was monitored at 214 nm.

The fraction with biological activity was separated into one major peak  
15 plus other smaller components. Western blot of this peak onto PVDF membrane revealed three major bands of molecular weights 14 Kd, 20 Kd and 26 Kd. These polypeptides were determined to have the following N-terminal sequences, respectively:

- (j) Xaa-Asp-Ser-Glu-Lys-Ser-Ala-Thr-Ile-Lys-Val-Thr-Asp-Ala-Ser; (SEQ ID No. 134)
- 20 (k) Ala-Gly-Asp-Thr-Xaa-Ile-Tyr-Ile-Val-Gly-Asn-Leu-Thr-Ala-Asp; (SEQ ID No. 135) and
- (l) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 136), wherein Xaa may be any amino acid.

Using the assays described above, these polypeptides were shown to induce  
25 proliferation and IFN-γ production in PBMC preparations. Figs. 1A and B show the results of such assays using PBMC preparations from a first and a second donor, respectively.

DNA sequences that encode the antigens designated as (a), (c), (d) and  
(g) above were obtained by screening a genomic *M. tuberculosis* library using <sup>32</sup>P end  
30 labeled degenerate oligonucleotides corresponding to the N-terminal sequence and

containing *M. tuberculosis* codon bias. The screen performed using a probe corresponding to antigen (a) above identified a clone having the sequence provided in SEQ ID No. 101. The polypeptide encoded by SEQ ID No. 101 is provided in SEQ ID No. 102. The screen performed using a probe corresponding to antigen (g) above  
5 identified a clone having the sequence provided in SEQ ID No. 52. The polypeptide encoded by SEQ ID No. 52 is provided in SEQ ID No. 53. The screen performed using a probe corresponding to antigen (d) above identified a clone having the sequence provided in SEQ ID No. 24, and the screen performed with a probe corresponding to antigen (c) identified a clone having the sequence provided in SEQ ID No. 25.

10 The above amino acid sequences were compared to known amino acid sequences in the gene bank using the DNA STAR system. The database searched contains some 173,000 proteins and is a combination of the Swiss, PIR databases along with translated protein sequences (Version 87). No significant homologies to the amino acid sequences for antigens (a)-(h) and (l) were detected.

15 The amino acid sequence for antigen (i) was found to be homologous to a sequence from *M. leprae*. The full length *M. leprae* sequence was amplified from genomic DNA using the sequence obtained from GENBANK. This sequence was then used to screen the *M. tuberculosis* library described below in Example 2 and a full length copy of the *M. tuberculosis* homologue was obtained (SEQ ID No. 99).

20 The amino acid sequence for antigen (j) was found to be homologous to a known *M. tuberculosis* protein translated from a DNA sequence. To the best of the inventors' knowledge, this protein has not been previously shown to possess T-cell stimulatory activity. The amino acid sequence for antigen (k) was found to be related to a sequence from *M. leprae*.

25 In the proliferation and IFN- $\gamma$  assays described above, using three PPD positive donors, the results for representative antigens provided above are presented in Table 1:

TABLE 1  
RESULTS OF PBMC PROLIFERATION AND IFN- $\gamma$  ASSAYS

Sequence	Proliferation	IFN- $\gamma$
(a)	+	-
(c)	+++	+++
(d)	++	++
(g)	+++	+++
(h)	+++	+++

- 5                    In Table 1, responses that gave a stimulation index (SI) of between 2 and 4 (compared to cells cultured in medium alone) were scored as +, an SI of 4-8 or 2-4 at a concentration of 1  $\mu$ g or less was scored as ++ and an SI of greater than 8 was scored as +++. The antigen of sequence (i) was found to have a high SI (+++) for one donor and lower SI (++ and +) for the two other donors in both proliferation and IFN- $\gamma$  assays.
- 10    These results indicate that these antigens are capable of inducing proliferation and/or interferon- $\gamma$  production.

EXAMPLE 2  
USE OF PATIENT SERA TO ISOLATE *M. TUBERCULOSIS* ANTIGENS

15

This example illustrates the isolation of antigens from *M. tuberculosis* lysate by screening with serum from *M. tuberculosis*-infected individuals.

- Dessicated *M. tuberculosis* H37Ra (Difco Laboratories) was added to a 2% NP40 solution, and alternately homogenized and sonicated three times. The
- 20    resulting suspension was centrifuged at 13,000 rpm in microfuge tubes and the supernatant put through a 0.2 micron syringe filter. The filtrate was bound to Macro Prep DEAE beads (BioRad, Hercules, CA). The beads were extensively washed with 20 mM Tris pH 7.5 and bound proteins eluted with 1M NaCl. The 1M NaCl elute was dialyzed overnight against 10 mM Tris, pH 7.5. Dialyzed solution was treated with

DNase and RNase at 0.05 mg/ml for 30 min. at room temperature and then with  $\alpha$ -D-mannosidase, 0.5 U/mg at pH 4.5 for 3-4 hours at room temperature. After returning to pH 7.5, the material was fractionated via FPLC over a Bio Scale-Q-20 column (BioRad). Fractions were combined into nine pools, concentrated in a Centriprep 10 (Amicon, Beverley, MA) and then screened by Western blot for serological activity using a serum pool from *M. tuberculosis*-infected patients which was not immunoreactive with other antigens of the present invention.

The most reactive fraction was run in SDS-PAGE and transferred to PVDF. A band at approximately 85 Kd was cut out yielding the sequence:

(m) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val: (SEQ ID No. 137), wherein Xaa may be any amino acid.

Comparison of this sequence with those in the gene bank as described above, revealed no significant homologies to known sequences.

### EXAMPLE 3

#### PREPARATION OF DNA SEQUENCES ENCODING *M. TUBERCULOSIS* ANTIGENS

This example illustrates the preparation of DNA sequences encoding *M. tuberculosis* antigens by screening a *M. tuberculosis* expression library with sera obtained from patients infected with *M. tuberculosis*, or with anti-sera raised against soluble *M. tuberculosis* antigens.

#### A. PREPARATION OF *M. TUBERCULOSIS* SOLUBLE ANTIGENS USING RABBIT ANTI-SERA

Genomic DNA was isolated from the *M. tuberculosis* strain H37Ra. The DNA was randomly sheared and used to construct an expression library using the Lambda ZAP expression system (Stratagene, La Jolla, CA). Rabbit anti-sera was generated against secretory proteins of the *M. tuberculosis* strains H37Ra, H37Rv and Erdman by immunizing a rabbit with concentrated supernatant of the *M. tuberculosis* cultures. Specifically, the rabbit was first immunized subcutaneously with 200  $\mu$ g of

protein antigen in a total volume of 2 ml containing 10 µg muramyl dipeptide (Calbiochem, La Jolla, CA) and 1 ml of incomplete Freund's adjuvant. Four weeks later the rabbit was boosted subcutaneously with 100 µg antigen in incomplete Freund's adjuvant. Finally, the rabbit was immunized intravenously four weeks later with 50 µg protein antigen. The anti-sera were used to screen the expression library as described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. Bacteriophage plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and the nucleotide sequences of the *M. tuberculosis* clones deduced.

Thirty two clones were purified. Of these, 25 represent sequences that have not been previously identified in human *M. tuberculosis*. Recombinant antigens were expressed and purified antigens used in the immunological analysis described in Example 1. Proteins were induced by IPTG and purified by gel elution, as described in Skeiky et al., *J. Exp. Med.* 181:1527-1537, 1995. Representative sequences of DNA molecules identified in this screen are provided in SEQ ID Nos.: 1-25. The corresponding predicted amino acid sequences are shown in SEQ ID Nos. 63-87.

On comparison of these sequences with known sequences in the gene bank using the databases described above, it was found that the clones referred to hereinafter as TbRA2A, TbRA16, TbRA18, and TbRA29 (SEQ ID Nos. 76, 68, 70, 75) show some homology to sequences previously identified in *Mycobacterium leprae* but not in *M. tuberculosis*. TbRA11, TbRA26, TbRA28 and TbDPEP (SEQ ID Nos.: 65, 73, 74, 53) have been previously identified in *M. tuberculosis*. No significant homologies were found to TbRA1, TbRA3, TbRA4, TbRA9, TbRA10, TbRA13, TbRA17, TbRa19, TbRA29, TbRA32, TbRA36 and the overlapping clones TbRA35 and TbRA12 (SEQ ID Nos. 63, 77, 81, 82, 64, 67, 69, 71, 75, 78, 80, 79, 66). The clone TbRa24 is overlapping with clone TbRa29.

The results of PBMC proliferation and interferon-γ assays performed on representative recombinant antigens, and using T-cell preparations from several different *M. tuberculosis*-immune patients, are presented in Tables 2 and 3, respectively.

**TABLE 2**  
**RESULTS OF PBMC PROLIFERATION TO REPRESENTATIVE SOLUBLE ANTIGENS**

Antigen	Patient												
	1	2	3	4	5	6	7	8	9	10	11	12	13
TbRa1	-	-	±	++	-	-	±	±	-	-	+	±	-
TbRa3	-	±	++	-	±	-	-	++	±	-	-	-	-
TbRa9	-	-	nt	nt	++	++	nt	nt	nt	nt	nt	nt	nt
TbRa10	-	-	±	±	±	+	nt	±	-	+	±	±	-
TbRa11	±	±	+	++	++	+	nt	-	++	++	++	±	nt
TbRa12	-	-	+	+	±	++	+	±	±	-	+	-	-
TbRa16	nt	nt	nt	nt	-	+	nt	nt	nt	nt	nt	nt	nt
TbRa24	nt	nt	nt	nt	-	-	nt	nt	nt	nt	nt	nt	nt
TbRa26	-	+	nt	nt	-	-	nt	nt	nt	nt	nt	nt	nt
TbRa29	nt	nt	nt	nt	-	-	nt	nt	nt	nt	nt	nt	nt
TbRa35	++	nt	++	++	++	++	nt	++	++	++	++	++	nt
TbRaB	nt	nt	nt	nt	-	-	nt	nt	nt	nt	nt	nt	nt
TbRaC	nt	nt	nt	nt	-	-	nt	nt	nt	nt	nt	nt	nt
TbRaD	nt	nt	nt	nt	-	-	nt	nt	nt	nt	nt	nt	nt
AAMK	-	-	±	-	-	-	nt	-	-	-	nt	±	nt
YY	-	-	-	-	-	-	nt	-	-	-	nt	+	nt
DPEP	-	+	-	++	-	-	nt	++	±	+	±	±	nt
Control	-	-	-	-	-	-	-	-	-	-	-	-	-

nt = not tested



In Tables 2 and 3, responses that gave a stimulation index (SI) of between 1.2 and 2 (compared to cells cultured in medium alone) were scored as  $\pm$ , a SI of 2-4 was scored as +, as SI of 4-8 or 2-4 at a concentration of 1  $\mu$ g or less was scored as ++ and an SI of greater than 8 was scored as +++. In addition, the effect of concentration on proliferation and interferon- $\gamma$  production is shown for two of the above antigens in the attached Figure. For both proliferation and interferon- $\gamma$  production, TbRa3 was scored as ++ and TbRa9 as +.

These results indicate that these soluble antigens can induce proliferation and/or interferon- $\gamma$  production in T-cells derived from an *M. tuberculosis*-immune individual.

B. USE OF PATIENT SERA TO IDENTIFY DNA SEQUENCES ENCODING *M. TUBERCULOSIS* ANTIGENS

The genomic DNA library described above, and an additional H37Rv library, were screened using pools of sera obtained from patients with active tuberculosis. To prepare the H37Rv library, *M. tuberculosis* strain H37Rv genomic DNA was isolated, subjected to partial *Sau*3A digestion and used to construct an expression library using the Lambda Zap expression system (Stratagene, La Jolla, Ca). Three different pools of sera, each containing sera obtained from three individuals with active pulmonary or pleural disease, were used in the expression screening. The pools were designated TbL, TbM and TbH, referring to relative reactivity with H37Ra lysate (*i.e.*, TbL = low reactivity, TbM = medium reactivity and TbH = high reactivity) in both ELISA and immunoblot format. A fourth pool of sera from seven patients with active pulmonary tuberculosis was also employed. All of the sera lacked increased reactivity with the recombinant 38 kD *M. tuberculosis* H37Ra phosphate-binding protein.

All pools were pre-adsorbed with *E. coli* lysate and used to screen the H37Ra and H37Rv expression libraries, as described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. Bacteriophage plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and the nucleotide sequences of the *M. tuberculosis* clones deduced.

Thirty two clones were purified. Of these, 31 represented sequences that had not been previously identified in human *M. tuberculosis*. Representative sequences of the DNA molecules identified are provided in SEQ ID Nos.: 26-51 and 105. Of these, TbH-8 and TbH-8-2 (SEQ. ID NO. 105) are non-contiguous DNA sequences  
5 from the same clone, and TbH-4 (SEQ. ID NO. 43) and TbH-4-FWD (SEQ. ID NO. 44) are non-contiguous sequences from the same clone. Amino acid sequences for the antigens hereinafter identified as Tb38-1, TbH-4, TbH-8, TbH-9, and TbH-12 are shown in SEQ ID Nos.: 88-92. Comparison of these sequences with known sequences in the gene bank using the databases identified above revealed no significant  
10 homologies to TbH-4, TbH-8, TbH-9 and TbM-3, although weak homologies were found to TbH-9. TbH-12 was found to be homologous to a 34 kD antigenic protein previously identified in *M. paratuberculosis* (Acc. No. S28515). Tb38-1 was found to be located 34 base pairs upstream of the open reading frame for the antigen ESAT-6 previously identified in *M. bovis* (Acc. No. U34848) and in *M. tuberculosis* (Sorensen  
15 et al., *Infec. Immun.* 63:1710-1717, 1995).

Probes derived from Tb38-1 and TbH-9, both isolated from an H37Ra library, were used to identify clones in an H37Rv library. Tb38-1 hybridized to Tb38-1F2, Tb38-1F3, Tb38-1F5 and Tb38-1F6 (SEQ. ID NOS. 112, 113, 116, 118, and 119). (SEQ ID NOS. 112 and 113 are non-contiguous sequences from clone Tb38-  
20 1F2.) Two open reading frames were deduced in Tb38-1F2; one corresponds to Tb37FL (SEQ. ID. NO. 114), the second, a partial sequence, may be the homologue of Tb38-1 and is called Tb38-IN (SEQ. ID NO. 115). The deduced amino acid sequence of Tb38-1F3 is presented in SEQ. ID. NO. 117. A TbH-9 probe identified three clones in the H37Rv library: TbH-9-FL (SEQ. ID NO. 106), which may be the homologue of TbH-9  
25 (R37Ra), TbH-9-1 (SEQ. ID NO. 108), and TbH-9-4 (SEQ. ID NO. 110), all of which are highly related sequences to TbH-9. The deduced amino acid sequences for these three clones are presented in SEQ ID NOS. 107, 109 and 111.

The results of T-cell assays performed on Tb38-1, ESAT-6 and other representative recombinant antigens are presented in Tables 4A, B and 5, respectively,  
30 below:

**TABLE 4A**  
**RESULTS OF PBMC PROLIFERATION TO REPRESENTATIVE ANTIGENS**

Antigen	Donor										
	1	2	3	4	5	6	7	8	9	10	11
Tb38.1	+++	+	-	-	-	++	-	+	-	++	+++
ESAT-6	+++	+	+	+	-	+	-	+	+	++	+++
TbH-9	++	++	-	++	±	±	++	++	++	++	++

5

**TABLE 4B**  
**RESULTS OF PBMC INTERFERON- $\gamma$  PRODUCTION TO REPRESENTATIVE ANTIGENS**

Antigen	Donor										
	1	2	3	4	5	6	7	8	9	10	11
Tb38.1	+++	+	-	+	+	+++	-	++	-	+++	+++
ESAT-6	+++	+	+	+	+-	+	-	+	+	+++	+++
TbH-9	++	++	-	+++	±	±	+++	+++	++	+++	++

10

**TABLE 5**  
**SUMMARY OF T-CELL RESPONSES TO REPRESENTATIVE ANTIGENS**

Antigen	Proliferation			Interferon- $\gamma$			total
	patient 4	patient 5	patient 6	patient 4	patient 5	patient 6	
TbH9	++	++	++	+++	++	++	13
TbM7	-	+	-	++	+	-	4
TbH5	-	+	+	++	++	++	8
TbL23	-	+	$\pm$	++	++	+	7.5
TbH4	-	++	$\pm$	++	++	$\pm$	7
- control	-	-	-	-	-	-	0

5

These results indicate that both the inventive *M. tuberculosis* antigens and ESAT-6 can induce proliferation and/or interferon- $\gamma$  production in T-cells derived from an *M. tuberculosis*-immune individual. To the best of the inventors' knowledge, ESAT-6 has not been previously shown to stimulate human immune responses

10

A set of six overlapping peptides covering the amino acid sequence of the antigen Tb38-1 was constructed using the method described in Example 4. The sequences of these peptides, hereinafter referred to as pep1-6, are provided in SEQ ID Nos. 93-98, respectively. The results of T-cell assays using these peptides are shown in Tables 6 and 7. These results confirm the existence, and help to localize T-cell epitopes within Tb38-1 capable of inducing proliferation and interferon- $\gamma$  production in T-cells derived from an *M. tuberculosis* immune individual.

15

**TABLE 6**  
**RESULTS OF PBMC PROLIFERATION TO TB38-1 PEPTIDES**

Peptide	Patient												
	1	2	3	4	5	6	7	8	9	10	11	12	13
	-	-	-	-	±	-	-	-	-	±	-	-	+
pep1	±	-	-	-	±	-	-	-	±	±	-	-	+
pep2	-	-	-	-	-	-	-	-	±	-	-	-	+
pep3	++	-	-	-	-	-	-	-	±	-	-	-	±
pep4	++	±	-	-	-	-	+	-	±	±	-	-	+
pep5	-	++	-	-	-	-	+	-	±	-	-	-	+
Control	-	-	-	-	-	-	-	-	-	+	-	-	-



#### EXAMPLE 4

##### PURIFICATION AND CHARACTERIZATION OF A POLYPEPTIDE FROM TUBERCULIN PURIFIED PROTEIN DERIVATIVE

5

An *M. tuberculosis* polypeptide was isolated from tuberculin purified protein derivative (PPD) as follows.

PPD was prepared as published with some modification (Seibert, F. et al., Tuberculin purified protein derivative. Preparation and analyses of a large quantity  
10 for standard. The American Review of Tuberculosis 44:9-25, 1941).

*M. tuberculosis* Rv strain was grown for 6 weeks in synthetic medium in roller bottles at 37°C. Bottles containing the bacterial growth were then heated to 100° C in water vapor for 3 hours. Cultures were sterile filtered using a 0.22 µ filter and the liquid phase was concentrated 20 times using a 3 kD cut-off membrane. Proteins were  
15 precipitated once with 50% ammonium sulfate solution and eight times with 25% ammonium sulfate solution. The resulting proteins (PPD) were fractionated by reverse phase liquid chromatography (RP-HPLC) using a C18 column (7.8 x 300 mM; Waters, Milford, MA) in a Biocad HPLC system (Perseptive Biosystems, Framingham, MA). Fractions were eluted from the column with a linear gradient from 0-100% buffer (0.1%  
20 TFA in acetonitrile). The flow rate was 10 ml/minute and eluent was monitored at 214 nm and 280 nm.

Six fractions were collected, dried, suspended in PBS and tested individually in *M. tuberculosis*-infected guinea pigs for induction of delayed type hypersensitivity (DTH) reaction. One fraction was found to induce a strong DTH  
25 reaction and was subsequently fractionated further by RP-HPLC on a microbore Vydac C18 column (Cat. No. 218TP5115) in a Perkin Elmer/Applied Biosystems Division Model 172 HPLC. Fractions were eluted with a linear gradient from 5-100% buffer (0.05% TFA in acetonitrile) with a flow rate of 80 µl/minute. Eluent was monitored at 215 nm. Eight fractions were collected and tested for induction of DTH in *M.*  
30 *tuberculosis*-infected guinea pigs. One fraction was found to induce strong DTH of

about 16 mm induration. The other fractions did not induce detectable DTH. The positive fraction was submitted to SDS-PAGE gel electrophoresis and found to contain a single protein band of approximately 12 kD molecular weight.

This polypeptide, herein after referred to as DPPD, was sequenced from the amino terminal using a Perkin Elmer/Applied Biosystems Division Procise 492 protein sequencer as described above and found to have the N-terminal sequence shown in SEQ ID No.: 129. Comparison of this sequence with known sequences in the gene bank as described above revealed no known homologies. Four cyanogen bromide fragments of DPPD were isolated and found to have the sequences shown in SEQ ID Nos.: 130-133.

The ability of the antigen DPPD to stimulate human PBMC to proliferate and to produce IFN- $\gamma$  was assayed as described in Example 1. As shown in Table 8, DPPD was found to stimulate proliferation and elicit production of large quantities of IFN- $\gamma$ ; more than that elicited by commercial PPD.

TABLE 8

RESULTS OF PROLIFERATION AND INTERFERON- $\gamma$  ASSAYS TO DPPD

PBMC Donor	Stimulator	Proliferation (CPM)	IFN- $\gamma$ (OD <sub>450</sub> )
A	Medium	1,089	0.17
	PPD (commercial)	8,394	1.29
	DPPD	13,451	2.21
B	Medium	450	0.09
	PPD (commercial)	3,929	1.26
	DPPD	6,184	1.49
C	Medium	541	0.11
	PPD (commercial)	8,907	0.76
	DPPD	23,024	>2.70

EXAMPLE 5SYNTHESIS OF SYNTHETIC POLYPEPTIDES

5

Polypeptides may be synthesized on a Millipore 9050 peptide synthesizer using Fmoc chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray mass spectrometry and by amino acid analysis.

20

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purpose of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

- (i) APPLICANTS: Corixa Corporation
- (ii) TITLE OF INVENTION: COMPOUNDS AND METHODS FOR IMMUNOTHERAPY  
AND DIAGNOSIS OF TUBERCULOSIS
- (iii) NUMBER OF SEQUENCES: 137
- (iv) CORRESPONDENCE ADDRESS:
  - (A) ADDRESSEE: SEED and BERRY LLP
  - (B) STREET: 6300 Columbia Center, 701 Fifth Avenue
  - (C) CITY: Seattle
  - (D) STATE: Washington
  - (E) COUNTRY: USA
  - (F) ZIP: 98104-7092
- (v) COMPUTER READABLE FORM:
  - (A) MEDIUM TYPE: Floppy disk
  - (B) COMPUTER: IBM PC compatible
  - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
  - (D) SOFTWARE: PatentIn Release #1.0. Version #1.30
- (vi) CURRENT APPLICATION DATA:
  - (A) APPLICATION NUMBER:
  - (B) FILING DATE: 27-AUG-1996
  - (C) CLASSIFICATION:
- (viii) ATTORNEY/AGENT INFORMATION:
  - (A) NAME: Maki, David J.
  - (B) REGISTRATION NUMBER: 31,392
  - (C) REFERENCE/DOCKET NUMBER: 210121.411PC
- (ix) TELECOMMUNICATION INFORMATION:
  - (A) TELEPHONE: (206) 622-4900
  - (B) TELEFAX: (206) 682-6031

## (2) INFORMATION FOR SEQ ID NO:1:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 766 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CGAGGCACCG GTAGTTTGAA CCAAACGCAC AATCGACGGG CAAACGAACG GAAGAACACA	60
ACCATGAAGA TGGTGAAATC GATCGCCGCA GGTCTGACCG CCGCGGCTGC AATCGGCGCC	120
GCTGCGGCCG GTGTGACTTC GATCATGGCT GGCGGCCCGG TCGTATACCA GATGCAGCCG	180
GTCGTCTTCG GCGCGCCACT GCCGTTGGAC CCGGCATCCG CCCCTGACGT CCCGACCGCC	240
GCCCAGTTGA CCAGCCTGCT CAACAGCCTC GCCGATCCCA ACGTGTCGTT TGCGAACAAG	300
GGCAGTCTGG TCGAGGGCGG CATCGGGGGC ACCGAGGCGC GCATCGCCGA CCACAAGCTG	360
AAGAAGGCCG CCGAGCACGG GGATCTGCCG CTGTCGTTCA GCGTGACGAA CATCCAGCCG	420
GCGGCCGCCG GTTCGGCCAC CGCCGACGTT TCCGTCTCGG GTCCGAAGCT CTCGTCGCCG	480
GTCACGCAGA ACGTCACGTT CGTGAATCAA GGCGGCTGGA TGCTGTCACG CGCATCGGCG	540
ATGGAGTTGC TGCAGGCCGC AGGGNAACTG ATTGGCGGGC CGGNTTCAGC CCGCTGTTCA	600
GCTACGCCGC CCGCCTGGTG ACGCGTCCAT GTCGAACACT CGCGCGTGTA GCACGGTGCG	660
GTNTGCGCAG GGNCGCACGC ACCGCCCGGT GCAAGCCGTC CTCGAGATAG GTGGTGNCTC	720
GNCACCAGNG ANCACCCCN NNTCGNCNNT TCTCGNTGNT GNATGA	766

## (2) INFORMATION FOR SEQ ID NO:2:

- (A) LENGTH: 752 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

ATGCATCACC ATCACCATCA CGATGAAGTC ACGGTAGAGA CGACCTCCGT CTTCCGCGCA	60
GACTTCCTCA GCGAGCTGGA CGCTCCTGCG CAAGCGGGTA CGGAGAGCGC GGTCTCCGGG	120
GTGGAAGGGC TCCCGCCGGG CTCGGCGTTG CTGGTAGTCA AACGAGGCCC CAACGCCGGG	180
TCCCGGTTCC TACTCGACCA AGCCATCACG TCGGCTGGTC GGCATCCCGA CAGCGACATA	240
TTTCTCGACG ACGTGACCGT GAGCCGTGCG CATGCTGAAT TCCGGTTGGA AAACAACGAA	300
TTCAATGTCG TCGATGTCGG GAGTCTCAAC GGCACCTACG TCAACCGCGA GCCCGTGGAT	360
TCGGCGGTGC TGGCGAACGG CGACGAGGTC CAGATCGGCA AGCTCCGGTT GGTGTTCTTG	420
ACCGGACCCA AGCAAGGCGA GGATGACGGG AGTACCGGGG GCCCGTGAGC GCACCCGATA	480
GCCCCGCGCT GGCCGGGATG TCGATCGGGG CGGTCCTCCG ACCTGCTACG ACCGGATTTT	540
CCCTGATGTC CACCATCTCC AAGATTCGAT TCTTGGGAGG CTTGAGGGTC NGGGTGACCC	600
CCCCGCGGGC CTCATTCNGG GGTNTCGGCN GGTTTCACCC CNTACCNACT GCCNCCCGGN	660
TTGCNAATTC NTTCTTCNCT GCCCNAAAG GGACCNTTAN CTTGCCGCTN GAAANGGTNA	720
TCCNGGGCCC NTCCTNGAAN CCCCNTCCCC CT	752

## (2) INFORMATION FOR SEQ ID NO:3:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 813 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CATATGCATC ACCATCACCA TCACACTTCT AACCGCCCAG CGCGTCGGGG GCGTCGAGCA	60
CCACGCGACA CCGGGCCCCGA TCGATCTGCT AGCTTGAGTC TGGTCAGGCA TCGTCGTCAG	120
CAGCGCGATG CCCTATGTTT GTCGTCGACT CAGATATCGC GGCAATCCAA TCTCCCGCCT	180
GCGGCCGGCG GTGCTGCAAA CTACTCCCGG AGGAATTTTCG ACGTGCGCAT CAAGATCTTC	240
ATGCTGGTCA CGGCTGTCGT TTTGCTCTGT TGTTCGGGTG TGGCCACGGC CGCGCCCAAG	300
ACCTACTGCG AGGAGTTGAA AGGCACCGAT ACCGGCCAGG CGTGCCAGAT TCAAATGTCC	360
GACCCGGCCT ACAACATCAA CATCAGCCTG CCCAGTTACT ACCCCGACCA GAAGTCGCTG	420
GAAAATTACA TCGCCCAGAC GCGCGACAAG TTCCTCAGCG CGGCCACATC GTCCACTCCA	480
CGCGAAGCCC CCTACGAATT GAATATCACC TCGGCCACAT ACCAGTCCGC GATACCGCCG	540
CGTGGTACGC AGGCCGTGGT GCTCAMGGTC TACCACAACG CCGGCGGCAC GCACCCAACG	600
ACCACGTACA AGGCCTTCGA TTGGGACCAG GCCTATCGCA AGCCAATCAC CTATGACACG	660
CTGTGGCAGG CTGACACCGA TCCGCTGCCA GTCGTCTTCC CCATTGTTGC AAGGTGAACT	720
GAGCAACGCA GACCGGGACA ACWGGTATCG ATAGCCGCCN AATGCCGGCT TGGAACCCNG	780
TGAAATTATC ACAACTTCGC AGTCACNAAA NAA	813

## (2) INFORMATION FOR SEQ ID NO:4:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 447 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

CGGTATGAAC	ACGGCCGCGT	CCGATAACTT	CCAGCTGTCC	CAGGGTGGGC	AGGGATTCGC	60
CATTCCGATC	GGGCAGGCGA	TGGCGATCGC	GGGCCAGATC	CGATCGGGTG	GGGGGTCACC	120
CACCGTTCAT	ATCGGGCCTA	CCGCCTTCCT	CGGCTTGGGT	GTTGTCGACA	ACAACGGCAA	180
CGGCGCACGA	GTCCAACGCG	TGGTCGGGAG	CGCTCCGGCG	GCAAGTCTCG	GCATCTCCAC	240
CGGCGACGTG	ATCACC GCGG	TCGACGGCGC	TCCGATCAAC	TCGGCCACCG	CGATGGCGGA	300
CGCGCTTAAC	GGGCATCATC	CCGGTGACGT	CATCTCGGTG	AACTGGCAAA	CCAAGTCGGG	360
CGGCACGCGT	ACAGGGAACG	TGACATTGGC	CGAGGGACCC	CCGGCCTGAT	TTCGTCGYGG	420
ATACCACCCG	CCGGCCGGCC	AATTGGA				447

## (2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 604 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GTCCCACTGC	GGTCGCCGAG	TATGTCGCCC	AGCAAATGTC	TGGCAGCCGC	CCAACGGAAT	60
CCGGTGATCC	GACGTCGCAG	GTTGTCGAAC	CCGCCGCCGC	GGAAGTATCG	GTCCATGCCT	120
AGCCCGGCGA	CGGCGAGCGC	CGGAATGGCG	CGAGTGAGGA	GGCGGGCAAT	TTGGCGGGGC	180
CCGGCGACGG	NGAGCGCCGG	AATGGCGCGA	GTGAGGAGGT	GGNCAGTCAT	GCCCAGNGTG	240
ATCCAATCAA	CCTGNATTCG	GNCTGNNGGN	CCATTTGACA	ATCGAGGTAG	TGAGCGCAAA	300
TGAATGATGG	AAAACGGGNG	GNGACGTCCG	NTGTTCTGGT	GGTGNTAGGT	GNCTGNCTGG	360

NGTNGNGGNT ATCAGGATGT TCTTCGNCGA AANCTGATGN CGAGGAACAG GGTGTNCCCG	420
NNANNCCNAN GGNGTCCNAN CCCNNNTCC TCGNCGANAT CANANAGNCG NTTGATGNGA	480
NAAAAGGGTG GANCAGNNNN AANTNGNGGN CCNAANAANC NNNANNGNNG NNAGNTNGNT	540
NNNTNTTNNC ANNNNNNTG NNGNNGNNCN NNNCAANCNN NTNNNGNAA NNGGNTTNTT	600
NAAT	604

## (2) INFORMATION FOR SEQ ID NO:6:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 633 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

TTGCANGTCG AACCACCTCA CTAAAGGGAA CAAAAGCTNG AGCTCCACCG CGGTGGCGGC	60
CGCTCTAGAA CTAGTGKATM YYYCKGGCTG CAGSAATYCG GYACGAGCAT TAGGACAGTC	120
TAACGGTCCT GTTACGGTGA TCGAATGACC GACGACATCC TGCTGATCGA CACCGACGAA	180
CGGGTGCGAA CCCTCACCT CAACCGGCCG CAGTCCCGYA ACGCGCTCTC GGCGGCGCTA	240
CGGGATCGGT TTTTCGCGGY GTTGGYCGAC GCCGAGGYCG ACGACGACAT CGACGTCGTC	300
ATCCTCACCG GYGCCGATCC GGTGTTCTGC GCCGACTGG ACCTCAAGGT AGCTGGCCGG	360
GCAGACCGCG CTGCCGGACA TCTCACCGCG GTGGGCGGCC ATGACCAAGC CGGTGATCGG	420
CGCGATCAAC GGCGCCGCGG TCACCGGCGG GCTCGAACTG GCGCTGTACT GCGACATCCT	480
GATCGCCTCC GAGCAGCCCC GCTTCGNCGA CACCCACGCC CGGGTGGGGC TGCTGCCCAC	540
CTGGGGACTC AGTGTGTGCT TGCCGAAAA GGTGCGCATC GGNCTGGGCC GGTGGATGAG	600
CCTGACCGGC GACTACCTGT CCGTGACCGA CGC	633

## (2) INFORMATION FOR SEQ ID NO:7:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1362 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CGACGACGAC GGC GCCGAG AGCGGGCGCG AACGGCGATC GACGCGGCC TGGCCAGAGT	60
CGGCACCACC CAGGAGGGAG TCGAATCATG AAATTTGTCA ACCATATTGA GCCCGTCGCG	120
CCCCGCCGAG CCGGCGGGCG GGTGCGCGAG GTCTATGCCG AGGCCCCGCC CGAGTTCGGC	180
CGGCTGCCCC AGCCGCTCGC CATGCTGTCC CCGGACGAGG GACTGCTCAC CGCCGGCTGG	240
GCGACGTTGC GCGAGACACT GCTGGTGGGC CAGGTGCCGC GTGGCCGCAA GGAAGCCGTC	300
GCCGCCGCCG TCGCGGCCAG CCTGCGCTGC CCCTGGTGCG TCGACGCACA CACCACCATG	360
CTGTACGCGG CAGGCCAAAC CGACACCGCC GCGGCGATCT TGGCCGGCAC AGCACCTGCC	420
GCCGGTGACC CGAACGCGCC GTATGTGGCG TGGGCGGCAG GAACCGGGAC ACCGGCGGGA	480
CCGCCGGCAC CGTTCGGCCC GGATGTCGCC GCCGAATACC TGGGCACCGC GGTGCAATTC	540
CACTTCATCG CACGCCTGGT CCTGGTGCTG CTGGACGAAA CCTTCCTGCC GGGGGGCCCG	600
CGCGCCCAAC AGCTCATGCG CCGCGCCGGT GGA CTGGTGT TCGCCCGCAA GGTGCGCGCG	660
GAGCATCGGC CGGGCCGCTC CACCCGCCGG CTCGAGCCGC GAACGCTGCC CGACGATCTG	720
GCATGGGCAA CACCGTCCGA GCCCATAGCA ACCGCGTTCTG CCGCGCTCAG CCACCACCTG	780
GACACCGCGC CGCACCTGCC GCCACCGACT CGTCAGGTGG TCAGGCGGGT CGTGGGGTCG	840
TGGCACGGCG AGCCAATGCC GATGAGCAGT CGCTGGACGA ACGAGCACAC CGCCGAGCTG	900

CCCGCCGACC TGCACGCGCC CACCCGTCTT GCCCTGCTGA CCGGCCTGGC CCCGCATCAG	960
GTGACCGACG ACGACGTCGC CGCGGCCCGA TCCCTGCTCG ACACCGATGC GGCCTGGTT	1020
GGCGCCCTGG CTTGGGCCGC CTTCACCGCC GCGCGGCGCA TCGGCACCTG GATCGGCGCC	1080
GCCGCCGAGG GCCAGGTGTC GCGGCAAAAC CCGACTGGGT GAGTGTGCGC GCCCTGTCGG	1140
TAGGGTGTCA TCGCTGGCCC GAGGGATCTC GCGGCGGCGA ACGGAGGTGG CGACACAGGT	1200
GGAAGCTGCG CCCACTGGCT TCGCCCCAA CGCGTCGTG GCGTTCGGT TGGCCGCACT	1260
GGCCGATCAG GTCGGCGCCG GCCCTTGGCC GAAGGTCCAG CTCAACGTGC CGTCACCGAA	1320
GGACCGGACG GTCACCGGGG GTCACCCTGC GCGCCAAGG AA	1362

## (2) INFORMATION FOR SEQ ID NO:8:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1458 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GCGACGACCC CGATATGCCG GGCACCGTAG CGAAAGCCGT CGCCGACGCA CTCGGGCGCG	60
GTATCGCTCC CGTTGAGGAC ATTCAGGACT GCGTGGAGGC CCGGCTGGGG GAAGCCGGTC	120
TGGATGACGT GGCCCGTGTT TACATCATCT ACCGGCAGCG GCGCGCCGAG CTGCGGACGG	180
CTAAGGCCTT GCTCGGCGTG CGGGACGAGT TAAAGCTGAG CTTGGCGGCC GTGACGGTAC	240
TGCGCGAGCG CTATCTGCTG CACGACGAGC AGGGCCGGCC GGCCGAGTCG ACCGGCGAGC	300
TGATGGACCG ATCGGCGCGC TGTGTCGCGG CGGCCGAGGA CCAGTATGAG CCGGGCTCGT	360
CGAGGCGGTG GGCCGAGCGG TTCGCCACGC TATTACGCAA CCTGGAATTC CTGCCGAATT	420
CGCCCACGTT GATGAACTCT GGCACCGACC TGGGACTGCT CGCCGGCTGT TTTGTTCTGC	480

CGATTGAGGA TTCGCTGCAA TCGATCTTTG CGACGCTGGG ACAGGCCGCC GAGCTGCAGC	540
GGGCTGGAGG CGGCACCGGA TATGCGTTCA GCCACCTGCG ACCCGCCGGG GATCGGGTGG	600
CCTCCACGGG CGGCACGGCC AGCGGACCGG TGTCGTTTCT ACGGCTGTAT GACAGTGCCG	660
CGGGTGTGGT CTCCATGGGC GGTGCGCGGC GTGGCGCCTG TATGGCTGTG CTTGATGTGT	720
CGCACCCGGA TATCTGTGAT TTCGTCACCG CCAAGGCCGA ATCCCCAGC GAGCTCCCGC	780
ATTTCAACCT ATCGGTTGGT GTGACCGACG CGTTCCTGCG GGCCGTCGAA CGCAACGGCC	840
TACACCGGCT GGTCAATCCG CGAACCGGCA AGATCGTCGC GCGGATGCCC GCCGCCGAGC	900
TGTTGACGC CATCTGCAA GCGCGCACG CCGGTGGCGA TCCCGGGCTG GTGTTTCTCG	960
ACACGATCAA TAGGGCAAAC CCGGTGCCGG GGAGAGGCCG CATCGAGGCG ACCAACCCGT	1020
GCGGGGAGGT CCCACTGCTG CCTTACGAGT CATGTAATCT CGGCTCGATC AACCTCGCCC	1080
GGATGCTCGC CGACGGTCGC GTCGACTGGG ACCGGCTCGA GGAGGTCGCC GGTGTGGCGG	1140
TGCGGTTTCT TGATGACGTC ATCGATGTCA GCCGCTACCC CTTCCCCGAA CTGGGTGAGG	1200
CGGCCCCGCG CACCCGCAAG ATCGGGCTGG GAGTCATGGG TTTGGCGGAA CTGCTTGCCG	1260
CACTGGGTAT TCCGTACGAC AGTGAAGAAG CCGTGCGGTT AGCCACCCGG CTCATGCGTC	1320
GCATACAGCA GGC GGCGCAC ACGGCATCGC GGAGGCTGGC CGAAGAGCGG GGCGCATTC	1380
CGGCGTTCAC CGATAGCCGG TTCGCGCGGT CGGGCCCGAG GCGCAACGCA CAGGTCACCT	1440
CCGTCGCTCC GACGGGCA	1458

## (2) INFORMATION FOR SEQ ID NO:9:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 862 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

ACGGTGTAAAT C̄GTGCTGGAT CTGGAACCGC GTGGCCCCGCT ACCTACCGAG ATCTACTGGC	60
GGCGCAGGGG GCTGGCCCTG GGCATCGCGG TCGTCGTAGT CGGGATCGCG GTGGCCATCG	120
TCATCGCCTT CGTCGACAGC AGCGCCGGTG CCAAACCGGT CAGCGCCGAC AAGCCGGCCT	180
CCGCCCAGAG CCATCCGGGC TCGCCGGCAC CCCAAGCACC CCAGCCGGCC GGGCAAACCG	240
AAGGTAACGC CGCCGCGGCC CCGCCGCAGG GCCAAAACCC CGAGACACCC ACGCCCACCG	300
CCGCGGTGCA GCCGCCGCCG GTGCTCAAGG AAGGGGACGA TTGCCCCGAT TCGACGCTGG	360
CCGTCAAAGG TTTGACCAAC GCGCCGCAGT ACTACGTCGG CGACCAGCCG AAGTTCACCA	420
TGGTGGTCAC CAACATCGGC CTGGTGTCTT GTAAACGCGA CGTTGGGGCC GCGGTGTTGG	480
CCGCCTACGT TTA CTGCTG GACAACAAGC GGTGTGGTC CAACCTGGAC TCGCGCCCT	540
CGAATGAGAC GCTGGTCAAG ACGTTTTCCC CCGGTGAGCA GGTAACGACC GCGGTGACCT	600
GGACCGGGAT GGGATCGGCG CCGCGCTGCC CATTGCCGCG GCCGGCGATC GGGCCGGGCA	660
CCTACAATCT CGTGGTACAA CTGGGCAATC TCGCTCGCT GCCGGTTCCG TTCATCCTGA	720
ATCAGCCGCC GCCGCCGCC GGGCCGGTAC CCGCTCCGGG TCCAGCGCAG GCGCCTCCGC	780
CGGAGTCTCC CGCGCAAGGC GGATAATTAT TGATCGCTGA TGGTCGATTC CGCCAGCTGT	840
GACAACCCCT CGCCTCGTGC CG	862

## (2) INFORMATION FOR SEQ ID NO:10:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 622 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

TTGATCAGCA CCGGCAAGGC GTCACATGCC TCCCTGGGTG TGCAGGTGAC CAATGACAAA	60
GACACCCCGG GCGCCAAGAT CGTCGAAGTA GTGGCCGGTG GTGCTGCCGC GAACGCTGGA	120
GTGCCGAAGG GCGTCGTTGT CACCAAGGTC GACGACCGCC CGATCAACAG CGCGGACGCG	180
TTGGTTGCCG CCGTGCGGTC CAAAGCGCCG GGCGCCACGG TGGCGCTAAC CTTTCAGGAT	240
CCCTCGGGCG GTAGCCGCAC AGTGCAAGTC ACCCTCGGCA AGGCGGAGCA GTGATGAAGG	300
TCGCCGCGCA GTGTTCAAAG CTCGGATATA CGGTGGCACC CATGGAACAG CGTGCGGAGT	360
TGGTGGTTGG CCGGGCACTT GTCGTCGTCG TTGACGATCG CACGGCGCAC GGCGATGAAG	420
ACCACAGCGG GCCGCTTGTC ACCGAGCTGC TCACCGAGGC CGGGTTTGTT GTCGACGGCG	480
TGGTGGCGGT GTCGGCCGAC GAGGTCGAGA TCCGAAATGC GCTGAACACA GCGGTGATCG	540
GCGGGGTGGA CCTGGTGGTG TCGGTCGGCG GGACCGNGT GACGNCTCGC GATGTCACCC	600
CGGAAGCCAC CCGNGACATT CT	622

## (2) INFORMATION FOR SEQ ID NO:11:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1200 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GGCGCAGCGG TAAGCCTGTT GGCCGCCGGC AACTGGTGT TGACAGCATG CGGCGGTGGC	60
ACCAACAGCT CGTCGTCAGG CGCAGGCGGA ACGTCTGGGT CGGTGCACTG CGGCGGCAAG	120
AAGGAGCTCC ACTCCAGCGG CTCGACCGCA CAAGAAAATG CCATGGAGCA GTTCGTCTAT	180

GCCTACGTGC GATCGTGCCC GGGCTACACG TTGGACTACA ACGCCAACGG GTCCGGTGCC	240
GGGGTGACCC AGTTTCTCAA CAACGAAACC GATTTTCGCCG GCTCGGATGT CCCGTTGAAT	300
CCGTCGACCG GTCAACCTGA CCGGTCGGCG GAGCGGTGCG GTTCCCCGGC ATGGGACCTG	360
CCGACGGTGT TCGGCCCCGAT CGCGATCACC TACAATATCA AGGGCGTGAG CACGCTGAAT	420
CTTGACGGAC CCACTACCGC CAAGATTTTC AACGGCACCA TCACCGTGTG GAATGATCCA	480
CAGATCCAAG CCCTCAACTC CGGCACCGAC CTGCCGCCAA CACCGATTAG CGTTATCTTC	540
CGCAGCGACA AGTCCGGTAC GTCGGACAAC TTCCAGAAAT ACCTCGACGG TGTATCCAAC	600
GGGGCGTGGG GCAAAGGCGC CAGCGAAACG TTCAGCGGGG GCGTCGGCGT CGGCGCCAGC	660
GGGAACAACG GAACGTCGGC CCTACTGCAG ACGACCGACG GGTGATCAC CTACAACGAG	720
TGGTCGTTTG CGGTGGGTAA GCAGTTGAAC ATGGCCCAGA TCATCACGTC GGCGGGTCCG	780
GATCCAGTGG CGATCACCAC CGAGTCGGTC GGTAAGACAA TCGCCGGGGC CAAGATCATG	840
GGACAAGGCA ACGACCTGGT ATTGGACACG TCGTCGTTCT ACAGACCCAC CCAGCCTGGC	900
TCTTACCCGA TCGTGCTGGC GACCTATGAG ATCGTCTGCT CGAAATACCC GGATGCGACG	960
ACCGGTACTG CGGTAAGGGC GTTTATGCAA GCCGCGATTG GTCCAGGCCA AGAAGGCCTG	1020
GACCAATACG GCTCCATTCC GTTGCCCCAA TC GTTCCAAG CAAAATTGGC GGCCGCGGTG	1080
AATGCTATTT CTTGACCTAG TGAAGGGAAT TCGACGGTGA GCGATGCCGT TCCGCAGGTA	1140
GGGTCGCAAT TTGGGCCGTA TCAGCTATTG CGGCTGCTGG GCCGAGGCGG GATGGGCGAG	1200

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1155 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GCAAGCAGCT G <sup>~</sup> CAGGTCGTG CTGTTCGACG AACTGGGCAT GCCGAAGACC AAACGCACCA	60
AGACCGGCTA CACCACGGAT GCCGACGCGC TGCAGTCGTT GTTCGACAAG ACCGGGCATC	120
CGTTTCTGCA ACATCTGCTC GCCCACC GCG ACGTCACCCG GCTCAAGGTC ACCGTCGACG	180
GGTTGCTCCA AGCGGTGGCC GCCGACGGCC GCATCCACAC CACGTTCAAC CAGACGATCG	240
CCGCGACCGG CCGGCTCTCC TCGACCGAAC CCAACCTGCA GAACATCCCG ATCCGCACCG	300
ACGCGGGCCG GCGGATCCGG GACGCGTTCTG TGGTCGGGGA CGGTTACGCC GAGTTGATGA	360
CGGCCGACTA CAGCCAGATC GAGATGCGGA TCATGGGGCA CCTGTCCGGG GACGAGGGCC	420
TCATCGAGGC GTTCAACACC GGGGAGGACC TGTATTCTGT CGTCGCGTCC CGGGTGTTCTG	480
GTGTGCCCAT CGACGAGGTC ACCGGCGAGT TCGGGCGCCG GGTCAAGGCG ATGTCCTACG	540
GGCTGGTTTA CGGGTTGAGC GCCTACGGCC TGTCGCAGCA GTTGAAAATC TCCACCGAGG	600
AAGCCAACGA GCAGATGGAC GCGTATTTCTG CCCGATTCGG CGGGGTGCGC GACTACCTGC	660
GCGCCGTAGT CGAGCGGGCC CGCAAGGACG GCTACACCTC GACGGTGCTG GGCCGTCGCC	720
GCTACCTGCC CGAGCTGGAC AGCAGCAACC GTCAAGTGCG GGAGGCCGCC GAGCGGGCGG	780
CGCTGAACGC GCCGATCCAG GGCAGCGCGG CCGACATCAT CAAGGTGGCC ATGATCCAGG	840
TCGACAAGGC GCTCAACGAG GCACAGCTGG CGTCGCGCAT GCTGCTGCAG GTCCACGACG	900
AGCTGCTGTT CGAAATCGCC CCCGGTGAAC GCGAGCGGGT CGAGGCCCTG GTGCGCGACA	960
AGATGGGCGG CGCTTACCCG CTCGACGTCC CGCTGGAGGT GTCGGTGGGC TACGGCCGCA	1020
GCTGGGACGC GGCGGCGCAC TGAGTGCCGA GCGTGATCT GGGGCGGGAA TTCGGCGATT	1080
TTTCCGCCCT GAGTTCACGC TCGGCGCAAT CGGGACCGAG TTTGTCCAGC GTGTACCCGT	1140
CGAGTAGCCT CGTCA	1155

## (2) INFORMATION FOR SEQ ID NO:13:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1771 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GAGCGCCGTC TGGTGTTTGA ACGGTTTTAC CGGTCGGCAT CGGCACGGGC GTTGCCGGGT	60
TCGGGCTCG GGTGGCGAT CGTCAAACAG GTGGTGCTCA ACCACGGCGG ATTGCTGCGC	120
ATCGAAGACA CCGACCCAGG CGGCCAGCCC CCTGGAACGT CGATTTACGT GCTGCTCCCC	180
GGCCGTCGGA TGCCGATTCC GCAGCTTCCC GGTGCGACGG CTGGCGCTCG GAGCACGGAC	240
ATCGAGAACT CTCGGGGTTC GCGAACGTT ATCTCAGTGG AATCTCAGTC CACGCGCGCA	300
ACCTAGTTGT GCAGTTACTG TTGAAAGCCA CACCCATGCC AGTCCACGCA TGGCCAAGTT	360
GGCCCGAGTA GTGGGCCTAG TACAGGAAGA GCAACCTAGC GACATGACGA ATCACCCACG	420
GTATTCGCCA CCGCCGCAGC AGCCGGGAAC CCCAGGTTAT GCTCAGGGGC AGCAGCAAAC	480
GTACAGCCAG CAGTTCGACT GGC GTTACCC ACCGTCCCCG CCCCCGCAGC CAACCCAGTA	540
CCGTCAACCC TACGAGGCGT TGGGTGGTAC CCGGCCGGGT CTGATACCTG GCGTGATTCC	600
GACCATGACG CCCCCTCCTG GGATGGTTCG CCAACGCCCT CGTGCAGGCA TGTTGGCCAT	660
CGGCGCGGTG ACGATAGCGG TGGTGTCCGC CGGCATCGGC GGC GCGGCCG CATCCCTGGT	720
CGGGTTCAAC CGGGCACCCG CCGGCCCCAG CGGCGGCCCA GTGGCTGCCA GCGCGGCGCC	780
AAGCATCCCC GCAGCAAACA TGCCGCCGGG GTCGGTCGAA CAGGTGGCGG CCAAGGTGGT	840
GCCCAGTGTC GTCATGTTGG AAACCGATCT GGGCCGCCAG TCGGAGGAGG GCTCCGGCAT	900
CATTCTGTCT GCCGAGGGGC TGATCTTGAC CAACAACCAC GTGATCGCGG CGGCCGCCAA	960

GCCTCCCCTG GGCAGTCCGC CGCCGAAAAC GACGGTAACC TTCTCTGACG GCGGGACCGC	1020
ACCCCTTCACG GTGGTGGGGG CTGACCCAC CAGTGATATC GCCGTGTCG GTGTTCAGGG	1080
CGTCTCCGGG CTCACCCCGA TCTCCCTGGG TTCCTCCTCG GACCTGAGGG TCGGTCAGCC	1140
GGTGCTGGCG ATCGGGTCGC CGCTCGGTTT GGAGGGCACC GTGACCACGG GGATCGTCAG	1200
CGCTCTCAAC CGTCCAGTGT CGACGACCGG CGAGGCCGGC AACCAGAACA CCGTGCTGGA	1260
CGCCATTCAG ACCGACGCCG CGATCAACCC CGGTAAGTCC GGGGGCGCGC TGGTGAACAT	1320
GAACGCTCAA CTCGTCGGAG TCAACTCGGC CATTGCCACG CTGGGCGCGG ACTCAGCCGA	1380
TGCGCAGAGC GGCTCGATCG GTCTCGGTTT TGCGATTCCA GTCGACCAGG CCAAGCGCAT	1440
CGCCGACGAG TTGATCAGCA CCGGCAAGGC GTCACATGCC TCCCTGGGTG TGCAGGTGAC	1500
CAATGACAAA GACACCCCGG GCGCCAAGAT CGTCGAAGTA GTGGCCGGTG GTGCTGCCGC	1560
GAACGCTGGA GTGCCGAAGG GCGTCGTTGT CACCAAGGTC GACGACCGCC CGATCAACAG	1620
CGCGGACGCG TTGGTTGCCG CCGTGCGGTC CAAAGCGCCG GCGCCACGG TGGCGCTAAC	1680
CTTTCAGGAT CCCTCGGGCG GTAGCCGCAC AGTGCAAGTC ACCCTCGGCA AGGCGGAGCA	1740
GTGATGAAGG TCGCCGCGCA GTGTTCAAAG C	1771

## (2) INFORMATION FOR SEQ ID NO:14:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1058 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

CTCCACCGCG GTGGCGGCCG CTCTAGAACT AGTGGATCCC CCGGGCTGCA GGAATTCGGC	60
ACGAGGATCC GACGTCGAG GTTGTCGAAC CCGCCGCCGC GGAAGTATCG GTCCATGCCT	120

AGCCCGGCGA CGGCGAGCGC CGGAATGGCG CGAGTGAGGA GGCGGGCAAT TTGGCGGGGC	180
CCGGCGACGG CGAGCGCCGG AATGGCGCGA GTGAGGAGGC GGGCAGTCAT GCCCAGCGTG	240
ATCCAATCAA CCTGCATTCG GCCTGCGGGC CCATTTGACA ATCGAGGTAG TGAGCGCAAA	300
TGAATGATGG AAAACGGGCG GTGACGTCCG CTGTTCTGGT GGTGCTAGGT GCCTGCCTGG	360
CGTTGTGGCT ATCAGGATGT TCTTCGCCGA AACCTGATGC CGAGGAACAG GGTGTTCCCG	420
TGAGCCCGAC GGC GTCCGAC CCCGCGCTCC TCGCCGAGAT CAGGCAGTCG CTTGATGCGA	480
CAAAAGGGTT GACCAGCGTG CACGTAGCGG TCCGAACAAC CGGGAAAGTC GACAGCTTGC	540
TGGGTATTAC CAGTGCCGAT GTCGACGTCC GGGCCAATCC GCTCGCGGCA AAGGGCGTAT	600
GCACCTACAA CGACGAGCAG GGTGTCCCGT TTCGGGTACA AGGCGACAAC ATCTCGGTGA	660
AACTGTTCGA CGACTGGAGC AATCTCGGCT CGATTTCTGA ACTGTCAACT TCACGCGTGC	720
TCGATCCTGC CGCTGGGGTG ACGCAGCTGC TGTCCGGTGT CACGAACCTC CAAGCGCAAG	780
GTACCGAAGT GATAGACGGA ATTTGACCA CCAAATCAC CGGGACCATC CCCGCGAGCT	840
CTGTCAAGAT GCTTGATCCT GGCGCCAAGA GTGCAAGGCC GGCGACCGTG TGGATTGCCC	900
AGGACGGCTC GCACCACCTC GTCCGAGCGA GCATCGACCT CGGATCCGGG TCGATTCAGC	960
TCACGCAGTC GAAATGGAAC GAACCCGTCA ACGTCGACTA GGCCGAAGTT GCGTCGACGC	1020
GTTGNTCGAA ACGCCCTTGT GAACGGTGTC AACGGNAC	1058

(2) INFORMATION FOR SEQ ID NO:15:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 542 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GAATTCGGCA CGAGAGGTGA TCGACATCAT CGGGACCAGC CCCACATCCT GGGAACAGGC	60
GGCGGCGGAG GCGGTCCAGC GGGCGCGGGA TAGCGTCGAT GACATCCGCG TCGCTCGGGT	120
CATTGAGCAG GACATGGCCG TGGACAGCGC CGGCAAGATC ACCTACCGCA TCAAGCTCGA	180
AGTGTCGTTT AAGATGAGGC CGGCGCAACC GCGCTAGCAC GGGCCGGCGA GCAAGACGCA	240
AAATCGCACG GTTTGCGGTT GATTCGTGCG ATTTTGTGTC TGCTCGCCGA GGCCTACCAG	300
GCGCGGCCCA GGTCCGCGTG CTGCCGTATC CAGGCGTGCA TCGCGATTCC GGCGGCCACG	360
CCGGAGTTAA TGCTTCGCGT CGACCCGAAC TGGGCGATCC GCCGGNGAGC TGATCGATGA	420
CCGTGGCCAG CCCGTCGATG CCCGAGTTGC CCGAGGAAAC GTGCTGCCAG GCCGGTAGGA	480
AGCGTCCGTA GGCGGCGGTG CTGACCGGCT CTGCCTGCGC CCTCAGTGCG GCCAGCGAGC	540
GG	542

## (2) INFORMATION FOR SEQ ID NO:16:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 913 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CGGTGCCGCC CGCGCCTCCG TTGCCCCCAT TGCCGCCGTC GCCGATCAGC TGCGCATCGC	60
CACCATCACC GCCTTTGCCG CCGGCACCGC CGGTGGCGCC GGGGCCGCCG ATGCCACCGC	120
TTGACCCTGG CCGCCGGCGC CGCCATTGCC ATACAGCACC CCGCCGGGGG CACCGTTACC	180
GCCGTCGCCA CCGTCGCCGC CGCTGCCGTT TCAGGCCGGG GAGGCCGAAT GAACCGCCGC	240
CAAGCCCGCC GCCGGCACCG TTGCCGCCTT TTCCGCCCGC CCCGCCGGCG CCGCCAATTG	300

CCGAACAGCC AMGCACCGTT GCCGCCAGCC CCGCCGCCGT TAACGGCGCT GCCGGGCGCC	360
GCCGCCGGAC CCGCCATTAC CGCCGTTCCC GTTCGGTGCC CCGCCGTTAC CGGCGCCGCC	420
GTTTGCCGCC AATATTCGGC GGGCACCGCC AGACCCGCCG GGGCCACCAT TGCCGCCGGG	480
CACCGAAACA ACAGCCCAAC GGTGCCGCCG GCCCGCCGT TTGCCGCCAT CACCGGCCAT	540
TCACCGCCAG CACCGCCGTT AATGTTTATG AACCCGGTAC CGCCAGCGCG GCCCTATTG	600
CCGGGCGCCG GAGNGCGTGC CCGCCGGCGC CGCCAACGCC CAAAAGCCCG GGGTTGCCAC	660
CGGCCCCGCC GGACCCACCG GTCCCGCCGA TCCCCCGTT GCCGCCGGTG CCGCCGCCAT	720
TGGTGCTGCT GAAGCCGTTA GCGCCGGTTC CGCSGGTTCC GGCGGTGGCG CCNTGGCCGC	780
CGGCCCCGCC GTTGCCGTAC AGCCACCCCC CGGTGGCGCC GTTGCCGCCA TTGCCGCCAT	840
TGCCGCCGTT GCCGCCATTG CCGCCGTTCC CGCCGCCACC GCCGGNTTGG CCGCCGGCGC	900
CGCCGGCGGC CGC	913

## (2) INFORMATION FOR SEQ ID NO:17:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1872 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GACTACGTTG GTGTAGAAAA ATCCTGCCGC CCGGACCCTT AAGGCTGGGA CAATTTCTGA	60
TAGTACCCC GACACAGGAG GTTACGGGAT GAGCAATTCG CGCCGCCGCT CACTCAGGTG	120
GTCATGGTTG CTGAGCGTGC TGGCTGCCGT CGGGCTGGGC CTGGCCACGG CGCCGGCCCA	180
GGCGGCCCCG CCGGCCTTGT CGCAGGACCG GTTCGCCGAC TTCCCCGCGC TGCCCTCGA	240

CCCGTCCGCG ATGGTCGCCC AAGTGGCGCC ACAGGTGGTC AACATCAACA CCAAACCTGGG	300
CTACAACAAC GCCGTGGGCG CCGGGACCGG CATCGTCATC GATCCCAACG GTGTCGTGCT	360
GACCAACAAC CACGTGATCG CGGGCGCCAC CGACATCAAT GCGTTCAGCG TCGGCTCCGG	420
CCAAACCTAC GGCCTCGATG TGGTCGGGTA TGACCGCACC CAGGATGTCG CGGTGCTGCA	480
GCTGCGCGGT GCCGGTGGCC TGCCGTCCGC GGCATCGGT GCGGGCGTCG CGGTTGGTGA	540
GCCCGTCGTC GCGATGGGCA ACAGCGGTGG GCAGGGCGGA ACGCCCCGTG CGGTGCCTGG	600
CAGGGTGGTC GCGCTCGGCC AAACCGTGCA GGCCTCGGAT TCGTGACCG GTGCCGAAGA	660
GACATTGAAC GGGTTGATCC AGTTCGATGC CGCAATCCAG CCCGGTGATT CGGGCGGGCC	720
CGTCGTCAAC GGCCTAGGAC AGGTGGTCGG TATGAACACG GCCGCGTCCG ATAACCTCCA	780
GCTGTCCCAG GGTGGGCAGG GATTCGCCAT TCCGATCGGG CAGGCGATGG CGATCGCGGG	840
CCAAATCCGA TCGGGTGGGG GGTCACCCAC CGTTCATATC GGGCCTACCG CCTTCCTCGG	900
CTTGGGTGTT GTCGACAACA ACGGCAACGG CGCACGAGTC CAACGCGTGG TCGGAAGCGC	960
TCCGGCGGCA AGTCTCGGCA TCTCCACCGG CGACGTGATC ACCGCGGTCG ACGGCGCTCC	1020
GATCAACTCG GCCACCGCGA TGGCGGACGC GCTTAACGGG CATCATCCCG GTGACGTCAT	1080
CTCGGTGAAC TGGCAAACCA AGTCGGGCGG CACGCGTACA GGGAACGTGA CATTGGCCGA	1140
GGGACCCCCG GCCTGATTTG TCGCGGATAC CACCCGCCGG CCGGCCAATT GGATTGGCGC	1200
CAGCCGTGAT TGCCGCGTGA GCCCCGAGT TCCGTCTCCC GTGCGCGTGG CATTGTGGAA	1260
GCAATGAACG AGGCAGAACA CAGCGTTGAG CACCCTCCCG TGCAGGGCAG TTACGTGCAA	1320
GGCGGTGTGG TCGAGCATCC GGATGCCAAG GACTTCGGCA GCGCCGCCGC CCTGCCCCGC	1380
GATCCGACCT GGTTTAAGCA CGCCGTCTTC TACGAGGTGC TGGTCCGGGC GTTCTTCGAC	1440
GCCAGCGCGG ACGGTTCCGN CGATCTGCGT GGAATCATCG ATCGCCTCGA CTACCTGCAG	1500
TGGCTTGGCA TCGACTGCAT CTGTTGCCGC CGTTCCTACG ACTACCGCT GCGCGACGGC	1560
GGTTACGACA TTCGCGACTT CTACAAGGTG CTGCCCCAAT TCGGCACCGT CGACGATTTT	1620

GTCGCCCTGG TCGACACCGC TCACCGGCGA GGTATCCGCA TCATCACCGA CCTGGTGATG	1680
AATCACACCT CGGAGTCGCA CCCCTGGTTT CAGGAGTCCC GCCGCGACCC AGACGGACCG	1740
TACGGTGACT ATTACGTGTG GAGCGACACC AGCGAGCGCT ACACCGACGC CCGGATCATC	1800
TTCGTCGACA CCGAAGAGTC GAACTGGTCA TTCGATCCTG TCCGCCGACA GTTNCTACTG	1860
GCACCGATTC TT	1872

## (2) INFORMATION FOR SEQ ID NO:18:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1482 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CTTCGCCGAA ACCTGATGCC GAGGAACAGG GTGTTCCCGT GAGCCCGACG GCGTCCGACC	60
CCGCGCTCCT CGCCGAGATC AGGCAGTCGC TTGATGCGAC AAAAGGGTTG ACCAGCGTGC	120
ACGTAGCGGT CCGAACAACC GGGAAAGTCG ACAGCTTGCT GGGTATTACC AGTGCCGATG	180
TCGACGTCCG GGCCAATCCG CTCGCGGCAA AGGGCGTATG CACCTACAAC GACGAGCAGG	240
GTGTCCCGTT TCGGGTACAA GGCGACAACA TCTCGGTGAA ACTGTTCGAC GACTGGAGCA	300
ATCTCGGCTC GATTTCTGAA CTGTCAACTT CACGCGTGCT CGATCCTGCC GCTGGGGTGA	360
CGCAGCTGCT GTCCGGTGTC ACGAACCTCC AAGCGCAAGG TACCGAAGTG ATAGACGGAA	420
TTTCGACCAC CAAAATCACC GGGACCATCC CCGCGAGCTC TGTCAAGATG CTTGATCCTG	480
GCGCCAAGAG TGCAAGGCCG GCGACCGTGT GGATTGCCCA GGACGGCTCG CACCACCTCG	540
TCCGAGCGAG CATCGACCTC GGATCCGGGT CGATTCAGCT CACGCAGTCG AAATGGAACG	600

AACCCGTCAA CGTCGACTAG GCCGAAGTTG CGTCGACGCG TTGCTCGAAA CGCCCTTGTG	660
AACGGTGTCA ACGGCACCCG AAAACTGACC CCCTGACGGC ATCTGAAAAT TGACCCCTTA	720
GACCGGGCGG TTGGTGGTTA TTCTTCGGTG GTTCCGGCTG GTGGGACGCG GCCGAGGTCG	780
CGGTCTTTGA GCCGGTAGCT GTCGCCTTTG AGGGCGACGA CTTCAGCATG GTGGACGAGG	840
CGGTGATCA TGGCGGCAGC AACGACGTCG TCGCCGCCGA AAACCTCGCC CCACCGGCCG	900
AAGGCCTTAT TGGACGTGAC GATCAAGCTG GCCCGCTCAT ACCGGGAGGA CACCAGCTGG	960
AAGAAGAGGT TGGCGGCCTC GGGCTCAAAC GGAATGTAAC CGACTTCGTC AACCACCAGG	1020
AGCGGATAGC GGCCAAACCG GGTGAGTTCG GCGTAGATGC GCCCGGCGTG GTGAGCCTCG	1080
GCGAACCGTG CTACCCATTC GCGGGCGGTG GCGAACAGCA CCCGATGACC GGCCTGACAC	1140
GCGCGTATCG CCAGGCCGAC CGCAAGATGA GTCTTCCCGG TGCCAGGCGG GGCCCAAAAA	1200
CACGACGTTA TCGCGGGCGG TGATGAAATC CAGGGTGCCC AGATGTGCGA TGGTGTGCGG	1260
TTTGAGGCCA CGAGCATGCT CAAAGTCGAA CTCTTCCAAC GACTTCCGAA CCGGGAAGCG	1320
GGCGGCGCGG ATGCGGCCCT CACCACCATG GGAATCCCGG GCTGACACTT CCCGCTGCAG	1380
GCAGGCGGCC AGGTATTCTT CGTGGCTCCA GTTCTCGGCG CGGGCGCGAT CGGCCAGCCG	1440
GGAACTGAC TCACGCAGGG TGGGAGCTTT CAATGCTCTT GT	1482

## (2) INFORMATION FOR SEQ ID NO:19:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 876 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GAATTCGGCA CGAGCCGGCG ATAGCTTCTG GGCCGCGGCC GACCAGATGG CTCGAGGGTT	60
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CGTGCTCGGG GCCACCGCCG GCGCACACAC CCTGACCGGT GAGGGCCTGC AACACGCCGA	120
CGGTCACTCG TTGCTGCTGG ACGCCACCAA CCCGGCGGTG GTTGCCTACG ACCCGGCCTT	180
CGCCTACGAA ATCGGCTACA TCGNGGAAAG CGGACTGGCC AGGATGTGCG GGGAGAACCC	240
GGAGAACATC TTCTTCTACA TCACCGTCTA CAACGAGCCG TACGTGCAGC CGCCGGAGCC	300
GGAGAACTTC GATCCCGAGG GCGTGCTGGG GGGTATCTAC CGNTATCACG CGGCCACCGA	360
GCAACGCACC AACAAGGNGC AGATCCTGGC CTCCGGGGTA GCGATGCCCC CGGCGCTGCG	420
GGCAGCACAG ATGCTGGCCG CCGAGTGGGA TGTGCGCGCC GACGTGTGGT CGGTGACCAG	480
TTGGGGCGAG CTAAACCGCG ACGGGGTGGT CATCGAGACC GAGAAGCTCC GCCACCCCGA	540
TCGGCCGGCG GCGTGCCCT ACGTGACGAG AGCGCTGGAG AATGCTCGGG GCCCGGTGAT	600
CGCGGTGTCG GACTGGATGC GCGCGGTCCC CGAGCAGATC CGACCGTGGG TGCCGGGCAC	660
ATACCTCACG TTGGGCACCG ACGGGTTCGG TTTTCCGAC ACTCGGCCCC CCGGTCGTCG	720
TTACTTCAAC ACCGACGCCG AATCCCAGGT TGGTCGCGGT TTTGGGAGGG GTTGGCCGGG	780
TCGACGGGTG AATATCGACC CATTCGGTGC CGGTCGTGGG CCGCCCGCCC AGTTACCCGG	840
ATTCGACGAA GGTGGGGGGT TCGCCCCGAN TAAGTT	876

## (2) INFORMATION FOR SEQ ID NO:20:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1021 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

ATCCCCCGG GCTGCAGGAA TTCGGCACGA GAGACAAAAT TCCACGCGTT AATGCAGGAA	60
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CAGATTCATA ACGAATTCAC AGCGGCACAA CAATATGTCG CGATCGCGGT TTATTTGAC	120
AGCGAAGACC TGCCGCAGTT GGCGAAGCAT TTTTACAGCC AAGCGGTCGA GGAACGAAAC	180
CATGCAATGA TGCTCGTGCA ACACCTGCTC GACCGCGACC TTCGTGTCGA AATTCCCGGC	240
GTAGACACGG TGCGAAACCA GTTCGACAGA CCCC GCGAGG CACTGGCGCT GGC GCTCGAT	300
CAGGAACGCA CAGTCACCGA CCAGGTCGGT CGGCTGACAG CGGTGGCCCG CGACGAGGGC	360
GATTTCTCTG GCGAGCAGTT CATGCAGTGG TTCTTGACAG AACAGATCGA AGAGGTGGCC	420
TTGATGGCAA CCCTGGTGCG GGTTGCCGAT CGGGCCGGGG CCAACCTGTT CGAGCTAGAG	480
AACTTCGTG CACGTGAAGT GGATGTGGCG CCGGCCGCAT CAGGCGCCCC GCACGCTGCC	540
GGGGGCCGCC TCTAGATCCC TGGGGGGGAT CAGCGAGTGG TCCCGTTGCG CCGCCCGTCT	600
TCCAGCCAGG CCTTGGTGCG GCCGGGGTGG TGAGTACCAA TCCAGGCCAC CCCGACCTCC	660
CGGNAAAAGT CGATGTCCTC GTACTCATCG ACGTTCCAGG AGTACACCGC CCGGCCCTGA	720
GCTGCCGAGC GGTCAACGAG TTGCGGATAT TCCTTTAACG CAGGCAGTGA GGGTCCCACG	780
GCGGTTGGCC CGACCGCCGT GGCCGCACTG CTGGTCAGGT ATCGGGGGGT CTTGGCGAGC	840
AACAACGTCG GCAGGAGGGG TGGAGCCCGC CGGATCCGCA GACCGGGGGG GCGAAAACGA	900
CATCAACACC GCACGGGATC GATCTGCGGA GGGGGGTGCG GGAATACCGA ACCGGTGTAG	960
GAGCGCCAGC AGTTGTTTTT CCACCAGCGA AGCGTTTTTCG GGTCATCGGN GGCNNTTAAG	1020
T	1021

## (2) INFORMATION FOR SEQ ID NO:21:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 321 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CGTGCCGACG <u>A</u> ACGGAAGAA CACAACCATG AAGATGGTGA AATCGATCGC CGCAGGTCTG	60
ACCGCCGCGG CTGCAATCGG CGCCGCTGCG GCCGGTGTGA CTTCGATCAT GGCTGGCGGN	120
CCGGTCGTAT ACCAGATGCA GCCGGTCGTC TTCGGCGCGC CACTGCCGTT GGACCCGGNA	180
TCCGCCCCTG ANGTCCCGAC CGCCGCCCAG TGGACCAGNC TGCTCAACAG NCTCGNCGAT	240
CCCAACGTGT CGTTTGNGAA CAAGGGNAGT CTGGTCGAGG GNNGNATCGG NGGNANCGAG	300
GGNGNGNATC GNCGANACA A	321

## (2) INFORMATION FOR SEQ ID NO:22:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 373 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

TCTTATCGGT TCCGGTTGGC GACGGGTTTT GGGNGCGGGT GGTTAACCCG CTCGGCCAGC	60
CGATCGACGG GCGCGGAGAC GTCGACTCCG ATACTCGGCG CGCGCTGGAG CTCCAGGCGC	120
CCTCGGTGGT GNACCGGCAA GGCGTGAAGG AGCCGTTGNA GACCGGGATC AAGGCGATTG	180
ACGCGATGAC CCCGATCGGC CGCGGGCAGC GCCAGCTGAT CATCGGGGAC CGCAAGACCG	240
GCAAAAACCG CCGTCTGTGT CGGACACCAT CCTCAAACCA GCGGGAAGAA CTGGGAGTCC	300
GGTGGATCCC AAGAAGCAGG TCGCCTTGTG TATACGTTGG CCATCGGGCA AGAAGGGGAA	360
CTTACCATCG CCG	373

## (2) INFORMATION FOR SEQ ID NO:23:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 352 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GTGACGCCGT GATGGGATTC CTGGGCGGGG CCGGTCCGCT GGCGGTGGTG GATCAGCAAC	60
TGGTTACCCG GGTGCCGCAA GGCTGGTCGT TTGCTCAGGC AGCCGCTGTG CCGGTGGTGT	120
TCTTGACGGC CTGGTACGGG TTGGCCGATT TAGCCGAGAT CAAGGCGGGC GAATCGGTGC	180
TGATCCATGC CCGTACCGGC GGTGTGGGCA TGGCGGCTGT GCAGCTGGCT CGCCAGTGGG	240
GCGTGGAGGT TTTCGTCACC GCCAGCCGTG GNAAGTGGGA CACGCTGCGC GCCATNGNGT	300
TTGACGACGA NCCATATCGG NGATTCCNC ACATNCGAAG TTCCGANGGA GA	352

## (2) INFORMATION FOR SEQ ID NO:24:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 726 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GAAATCCGCG TTCATTCCGT TCGACCAGCG GCTGGCGATA ATCGACGAAG TGATCAAGCC	60
GCGGTTGCGG GCGCTCATGG GTCACAGCGA GTAATCAGCA AGTTCTCTGG TATATCGCAC	120
CTAGCGTCCA GTTGCTTGCC AGATCGCTTT CGTACCGTCA TCGCATGTAC CGGTTGCGGT	180
GCCGCACGCT CATGCTGGCG GCGTGATCC TGGCCACGGG TGTGGCGGGT CTCGGGGTCTG	240

GCGCGCAGTC CGCAGCCCAA ACCGCGCCGG TGCCCGACTA CTACTGGTGC CCGGGGCAGC	300
CTTTCGACCC CGCATGGGGG CCCAACTGGG ATCCCTACAC CTGCCATGAC GACTTCCACC	360
GCGACAGCGA CGGCCCCGAC CACAGCCGCG ACTACCCCGG ACCCATCCTC GAAGGTCCCCG	420
TGCTTGACGA TCCCGGTGCT GCGCCGCCGC CCCC GGCTGC CGGTGGCGGC GCATAGCGCT	480
CGTTGACCGG GCCGCATCAG CGAATACGCG TATAAACCCG GGC GTGCCCGG CGGCAAGCTA	540
CGACCCCCGG CGGGGCAGAT TTACGCTCCC GTGCCGATGG ATCGCGCCGT CCGATGACAG	600
AAAATAGGCG ACGGTTTTTG CAACCGCTTG GAGGACGCTT GAAGGGAACC TGTCATGAAC	660
GGCGACAGCG CCTCCACCAT CGACATCGAC AAGGTTGTTA CCCGCACACC CGTTCGCCGG	720
ATCGTG	726

## (2) INFORMATION FOR SEQ ID NO:25:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 580 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

CGCGACGACG ACGAACGTCG GGCCACCAC CGCCTATGCG TTGATGCAGG CGACCGGGAT	60
GGTCGCCGAC CATATCCAAG CATGCTGGGT GCCCACTGAG CGACCTTTTG ACCAGCCGGG	120
CTGCCC GATG GCGGCCCCGGT GAAGTCATTG CGCCGGGGCT TGTGCACCTG ATGAACCCGA	180
ATAGGGAACA ATAGGGGGGT GATTTGGCAG TTCAATGTCG GGTATGGCTG GAAATCCAAT	240
GGCGGGGCAT GCTCGGCGCC GACCAGGCTC GCGCAGGCGG GCCAGCCCGA ATCTGGAGGG	300
AGCACTCAAT GCGGCGATG AAGCCCCGGA CCGGCGACGG TCCTTTGGAA GCAACTAAGG	360

AGGGGCGCGG CATTGTGATG CGAGTACCAC TTGAGGGTGG CGGTCGCCTG GTCGTCGAGC	420
TGACACCCGA CGAAGCCGCC GCACTGGGTG ACGAACTCAA AGGCGTTACT AGCTAAGACC	480
AGCCCAACGG CGAATGGTCG GCGTTACGCG CACACCTTCC GGTAGATGTC CAGTGTCTGC	540
TCGGCGATGT ATGCCCAGGA GAACTCTTGG ATACAGCGCT	580

## (2) INFORMATION FOR SEQ ID NO:26:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 160 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

AACGGAGGCG CCGGGGGTTT TGGCGGGGCC GGGGCGGTCTG GCGGCAACGG CGGGGCCGGC	60
GGTACCGCCG GGTTGTTCGG TGTCGGCGGG GCCGGTGGGG CCGGAGGCAA CGGCATCGCC	120
GGTGTCACGG GTACGTCGGC CAGCACACCG GGTGGATCCG	160

## (2) INFORMATION FOR SEQ ID NO:27:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 272 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

GACACCGATA CGATGGTGAT GTACGCCAAC GTTGTGACA CGCTCGAGGC GTTCACGATC	60
CAGCGCACAC CCGACGGCGT GACCATCGGC GATGCGGCCC CGTTCGCGGA GGCGGCTGCC	120

AAGGCGATGG GAATCGACAA GCTGCGGGTA ATTCATACCG GAATGGACCC CGTCGTCGCT	180
GAACGCGAAC AGTGGGACGA CGGCAACAAC ACGTTGGCGT TGGCGCCCGG TGTCGTTGTC	240
GCCTACGAGC GCAACGTACA GACCAACGCC CG	272

## (2) INFORMATION FOR SEQ ID NO:28:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 317 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GCAGCCGGTG GTTCTCGGAC TATCTGCGCA CGGTGACGCA GCGCGACGTG CGCGAGCTGA	60
AGCGGATCGA GCAGACGGAT CGCCTGCCGC GGTTCATGCG CTACCTGGCC GCTATCACCG	120
CGCAGGAGCT GAACGTGGCC GAAGCGGCGC GGGTCATCGG GGTGACGCG GGGACGATCC	180
GTTCGGATCT GGCCTGGTTC GAGACGGTCT ATCTGGTACA TCGCCTGCCC GCCTGGTCGC	240
GGAATCTGAC CGCGAAGATC AAGAAGCGGT CAAAGATCCA CGTCGTCGAC AGTGGCTTCG	300
CGGCCTGGTT GCGCGGG	317

## (2) INFORMATION FOR SEQ ID NO:29:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 182 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GATCGTGGAG CTGTGATGA ACAGCGTTGC CGGACGCGCG GCGGCCAGCA CGTCGGTGTA	60
GCAGCGCCGG ACCACCTCGC CGGTGGGCAG CATGGTGATG ACCACGTCGG CCTCGGCCAC	120
CGCTTCGGGC GCGCTACGAA ACACCGCGAC ACCGTGCGCG GCGGCGCCGG ACGCCGCCGT	180
GG	182

(2) INFORMATION FOR SEQ ID NO:30:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 308 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GATCGCGAAG TTTGGTGAGC AGGTGGTCGA CGCGAAAGTC TGGGCGCCTG CGAAGCGGGT	60
CGGCGTTCAC GAGGCGAAGA CACGCCTGTC CGAGCTGCTG CGGCTCGTCT ACGGCGGGCA	120
GAGGTTGAGA TTGCCCGCCG CGGCGAGCCG GTAGCAAAGC TTGTGCCGCT GCATCCTCAT	180
GAGACTCGGC GGTTAGGCAT TGACCATGGC GTGTACCGCG TGCCCGACGA TTTGGACGCT	240
CCGTTGTCAG ACGACGTGCT CGAACGCTTT CACCGGTGAA GCGCTACCTC ATCGACACCC	300
ACGTTTGG	308

(2) INFORMATION FOR SEQ ID NO:31:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 267 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

CCGACGACGA GCAACTCACG TGGATGATGG TCGGCAGCGG CATTGAGGAC GGAGAGAATC	60
CGGCCGAAGC TGCCGCGCGG CAAGTGCTCA TAGTGACCGG CCGTAGAGGG CTCCCCGAT	120
GGCACC GGAC TATTCTGGTG TGCCGCTGGC CGGTAAGAGC GGGTAAAAGA ATGTGAGGGG	180
ACACGATGAG CAATCACACC TACCGAGTGA TCGAGATCGT CGGGACCTCG CCCGACGGCG	240
TCGACGCGGC AATCCAGGGC GGTCTGG	267

## (2) INFORMATION FOR SEQ ID NO:32:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 189 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CTCGTGCCGA AAGAATGTGA GGGGACACGA TGAGCAATCA CACCTACCGA GTGATCGAGA	60
TCGTCGGGAC CTCGCCGAC GCGGTCGACG CGGCAATCCA GGGCGGTCTG GCGGAGCTG	120
CGCAGACCAT GCGCGCGCTG GACTGGTTCG AAGTACAGTC AATTCGAGGC CACCTGGTCG	180
ACGGAGCGG	189

## (2) INFORMATION FOR SEQ ID NO:33:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 851 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CTGCAGGGTG GCGTGGATGA GCGTCACCGC GGGGCAGGCC GAGCTGACCG CCGCCCAGGT	60
CCGGGTTGCT GCGGCGGCCT ACGAGACGGC GTATGGGCTG ACGGTGCCCC CGCCGGTGAT	120
CGCCGAGAAC CGTGCTGAAC TGATGATTCT GATAGCGACC AACCTCTTGG GGCAAAACAC	180
CCCGGCGATC GCGGTCAACG AGGCCGAATA CGGCGAGATG TGGGCCCAAG ACGCCGCCGC	240
GATGTTTGGC TACGCCGCGG CGACGGCGAC GGCGACGGCG ACGTTGCTGC CGTTCGAGGA	300
GGCGCCGGAG ATGACCAGCG CGGGTGGGCT CCTCGAGCAG GCCGCCGCGG TCGAGGAGGC	360
CTCCGACACC GCCGCGGCGA ACCAGTTGAT GAACAATGTG CCCCAGGCGC TGAAACAGTT	420
GGCCCAGCCC ACGCAGGGCA CCACGCCTTC TTCCAAGCTG GGTGGCCTGT GGAAGACGGT	480
CTCGCCGCAT CGGTCGCCGA TCAGCAACAT GGTGTCGATG GCCAACAACC ACATGTCGAT	540
GACCAACTCG GGTGTGTCTGA TGACCAACAC CTTGAGCTCG ATGTTGAAGG GCTTTGCTCC	600
GGCGGCGGCC GCCCAGGCCG TGCAAACCGC GGCGCAAAAC GGGGTCCGGG CGATGAGCTC	660
GCTGGGCAGC TCGCTGGGTT CTTCGGGTCT GGGCGGTGGG GTGGCCGCCA ACTTGGGTCTG	720
GGCGGCCTCG GTACGGTATG GTCACCGGGA TGGCGGAAAA TATGCANAGT CTGGTCGGCG	780
GAACGGTGGT CCGGCGTAAG GTTTACCCCC GTTTTCTGGA TGCGGTGAAC TTCGTCAACG	840
GAAACAGTTA C	851

## (2) INFORMATION FOR SEQ ID NO:34:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 254 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GATCGATCGG GCGGAAATTT GGACCAGATT CGCCTCCGGC GATAACCCAA TCAATCGAAC	60
CTAGATTTAT TCCGTCCAGG GGCCCGAGTA ATGGCTCGCA GGAGAGGAAC CTTACTGCTG	120
CGGGCACCTG TCGTAGGTCC TCGATACGGC GGAAGGCGTC GACATTTTCC ACCGACACCC	180
CCATCCAAAC GTTCGAGGGC CACTCCAGCT TGTGAGCGAG GCGACGCAGT CGCAGGCTGC	240
GCTTGGTCAA GATC	254

## (2) INFORMATION FOR SEQ ID NO:35:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 408 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

CGGCACGAGG ATCCTGACCG AAGCGGCCGC CGCCAAGGCG AAGTCGCTGT TGGACCAGGA	60
GGGACGGGAC GATCTGGCGC TGCGGATCGC GGTTCAGCCG GGGGGGTGCG CTGGATTGCG	120
CTATAACCTT TTCTTCGACG ACCGGACGCT GGATGGTGAC CAAACCGCGG AGTTCGGTGG	180
TGTCAGGTTG ATCGTGGACC GGATGAGCGC GCCGTATGTG GAAGGCGCGT CGATCGATTT	240
CGTCGACACT ATTGAGAAGC AAGGNTTCAC CATCGACAAT CCCAACGCCA CCGGCTCCTG	300
CGCGTGCGGG GATTCGTTCA ACTGATAAAA CGCTAGTACG ACCCCGCGGT GCGCAACACG	360
TACGAGCACA CCAAGACCTG ACCGCGCTGG AAAAGCAACT GAGCGATG	408

## (2) INFORMATION FOR SEQ ID NO:36:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 181 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GCGGTGTCGG CGGATCCGGC GGGTGGTTGA ACGGCAACGG CGGGGCCGGC GGGGCCGGCG	60
GGACCGGCGC TAACGGTGGT GCCGGCGGCA ACGCCTGGTT GTTCGGGGCC GGCGGGTCCG	120
GCGGNGCCGG CACCAATGGT GGNGTCGGCG GGTCCGGCGG ATTTGTCTAC GGCAACGGCG	180
G	181

(2) INFORMATION FOR SEQ ID NO:37:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 290 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

GCGGTGTCGG CGGATCCGGC GGGTGGTTGA ACGGCAACGG CGGTGTCGGC GGCCGGGGCG	60
GCGACGGCGT CTTTGCCGGT GCCGGCGGCC AGGGCGGCCT CGGTGGGCAG GGCGGCAATG	120
GCGGCGGCTC CACCGGCGGC AACGGCGGTC TTGGCGGCGC GGGCGGTGGC GGAGGCAACG	180
CCCCGGACGG CGGCTTCGGT GGCAACGGCG GTAAGGGTGG CCAGGGCGGN ATTGGCGGCG	240
GCACTCAGAG CGCGACCGGC CTCGGNGGTG ACGGCGGTGA CGGCGGTGAC	290

(2) INFORMATION FOR SEQ ID NO:38:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 34 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

GATCCAGTGG CATGGNGGGT GTCAGTGGAA GCAT 34

(2) INFORMATION FOR SEQ ID NO:39:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 155 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

GATCGCTGCT CGTCCCCCCC TTGCCGCCGA CGCCACCGGT CCCACCGTTA CCGAACAAGC 60  
TGGCGTGGTC GCCAGCACCC CCGGCACCGC CGACGCCGGA GTCGAACAAT GGCACCGTCG 120  
TATCCCCACC ATTGCCGCCG GNCCCACCGG CACCG 155

(2) INFORMATION FOR SEQ ID NO:40:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 53 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

ATGGCGTTCA CGGGGCGCCG GGGACCGGGC AGCCCGGNGG GGCCGGGGGG TGG 53

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 132 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

GATCCACCGC GGGTGCAGAC GGTGCCCCGCG GCGCCACCCC GACCAGCGGC GGCAACGGCG 60

GCACCGGCGG CAACGGCGCG AACGCCACCG TCGTCGGNGG GGCCGGCGGG GCCGGCGGCA 120

AGGGCGGCAA CG 132

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 132 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

GATCGGCGGC CGGNACGGNC GGGGACGGCG GCAAGGGCGG NAACGGGGGC GCCGNAGCCA 60

CCNGCCAAGA ATCCTCCGNG TCCNCCAATG GCGCGAATGG CGGACAGGGC GGCAACGGCG 120

GCANCGGCGG CA 132

## (2) INFORMATION FOR SEQ ID NO:43:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 702 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CGGCACGAGG ATCGGTACCC CGCGGCATCG GCAGCTGCCG ATTCGCCGGG TTTCCCCACC	60
CGAGGAAAGC CGCTACCAGA TGGCGCTGCC GAAGTAGGGC GATCCGTTCG CGATGCCGGC	120
ATGAACGGGC GGCATCAAAT TAGTGCAGGA ACCTTTCAGT TTAGCGACGA TAATGGCTAT	180
AGCACTAAGG AGGATGATCC GATATGACGC AGTCGCAGAC CGTGACGGTG GATCAGCAAG	240
AGATTTTGAA CAGGGCCAAC GAGGTGGAGG CCCCAGTGGC GGACCCACCG ACTGATGTCC	300
CCATCACACC GTGCGAACTC ACGGNGGNTA AAAACGCCGC CCAACAGNTG GTNTTGTCCG	360
CCGACAACAT GCGGGAATAC CTGGCGGCCG GTGCCAAAGA GCGGCAGCGT CTGGCGACCT	420
CGCTGCGCAA CGCGGCCAAG GNGTATGGCG AGGTTGATGA GGAGGCTGCG ACCGCGCTGG	480
ACAACGACGG CGAAGGAACT GTGCAGGCAG AATCGGCCGG GGCCGTCGGA GGGGACAGTT	540
CGGCCGAACT AACCGATACG CCGAGGGTGG CCACGGCCGG TGAACCCAAC TTCATGGATC	600
TCAAAGAAGC GGCAAGGAAG CTCGAAACGG GCGACCAAGG CGCATCGCTC GCGCACTGNG	660
GGGATGGGTG GAACACTTNC ACCCTGACGC TGCAAGGCGA CG	702

## (2) INFORMATION FOR SEQ ID NO:44:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 298 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

GAAGCCGCAG CGCTGTCGGG CGACGTGGCG GTCAAAGCGG CATCGCTCGG TGGCGGTGGA	60
GGCGGCGGGG TGCCGTCGGC GCCGTTGGGA TCCGCGATCG GGGGCGCCGA ATCGGTGCGG	120
CCCGCTGGCG CTGGTGACAT TGCCGGCTTA GGCCAGGGAA GGGCCGGCGG CGGCGCCGCG	180
CTGGGCGGCG GTGGCATGGG AATGCCGATG GGTGCCGCGC ATCAGGGACA AGGGGGCGCC	240
AAGTCCAAGG GTTCTCAGCA GGAAGACGAG GCGCTCTACA CCGAGGATCC TCGTGCCG	298

## (2) INFORMATION FOR SEQ ID NO:45:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1058 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CGGCACGAGG ATCGAATCGC GTCGCCGGGA GCACAGCGTC GCACTGCACC AGTGGAGGAG	60
CCATGACCTA CTCGCCGGGT AACCCCGGAT ACCCGCAAGC GCAGCCCGCA GGCTCCTACG	120
GAGGCGTCAC ACCCTCGTTC GCCCACGCCG ATGAGGGTGC GAGCAAGCTA CCGATGTACC	180
TGAACATCGC GGTGGCAGTG CTCGGTCTGG CTGCGTACTT CGCCAGCTTC GGCCCAATGT	240
TCACCCTCAG TACCGAACTC GGGGGGGGTG ATGGCGCAGT GTCCGGTGAC ACTGGGCTGC	300
CGGTCGGGGT GGCTCTGCTG GCTGCGCTGC TTGCCGGGGT GGTTCCTGGT CCTAAGGCCA	360
AGAGCCATGT GACGGTAGTT GCGGTGCTCG GGGTACTCGG CGTATTTCTG ATGGTCTCGG	420

CGACGTTTAA CAAGCCCAGC GCCTATTCGA CCGGTTGGGC ATTGTGGGTT GTGTTGGCTT	480
TCATCGTGTT CCAGGCGGTT GCGGCAGTCC TGGCGCTCTT GGTGGAGACC GGCGCTATCA	540
CCGCGCCGGC GCCGCGGCCC AAGTTCGACC CGTATGGACA GTACGGGCGG TACGGGCAGT	600
ACGGGCAGTA CGGGGTGAG CCGGGTGGGT ACTACGGTCA GCAGGGTGCT CAGCAGGCCG	660
CGGGACTGCA GTCGCCCAGC CCGCAGCAGT CTCCGCAGCC TCCCGGATAT GGGTCGAGT	720
ACGGCGGCTA TTCGTCCAGT CCGAGCCAAT CGGGCAGTGG ATACACTGCT CAGCCCCCGG	780
CCCAGCCGCC GGCGCAGTCC GGGTCGCAAC AATCGCACCA GGGCCCATCC ACGCCACCTA	840
CCGGCTTTCC GAGCTTCAGC CCACCACCAC CGGTCAGTGC CGGGACGGGG TCGCAGGCTG	900
GTTGGGCTCC AGTCAACTAT TCAAACCCCA GCGGGGGCGA GCAGTCGTCG TCCCCGGGG	960
GGGCGCCGGT CTAACCGGGC GTTCCCGCGT CCGGTCGCGC GTGTGCGCGA AGAGTGAACA	1020
GGGTGTCAGC AAGCGCGGAC GATCCTCGTG CCGAATTC	1058

## (2) INFORMATION FOR SEQ ID NO:46:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 327 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

CGGCACGAGA GACCGATGCC GCTACCCTCG CGCAGGAGGC AGGTAATTTT GAGCGGATCT	60
CCGGCGACCT GAAAACCCAG ATCGACCAGG TGGAGTCGAC GGCAGGTTCT TTGCAGGGCC	120
AGTGGCGCGG CGCGGCGGGG ACGGCCGCCC AGGCCGCGGT GGTGCGCTTC CAAGAAGCAG	180
CCAATAAGCA GAAGCAGGAA CTCGACGAGA TCTCGACGAA TATTCGTCAG GCCGGCGTCC	240
AATACTCGAG GGCCGACGAG GAGCAGCAGC AGGCGCTGTC CTCGCAAATG GGCTTCTGAC	300

CCGCTAATAC GAAAAGAAAC GGAGCAA

327

(2) INFORMATION FOR SEQ ID NO:47:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 170 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

CGGTCGCGAT GATGGCGTTG TCGAACGTGA CCGATTCTGT ACCGCCGTCTG TTGAGATCAA	60
CCAACAACGT GTTGGCGTCG GCAAATGTGC CGNACCCGTG GATCTCGGTG ATCTTGTTCT	120
TCTTCATCAG GAAGTGCACA CCGGCCACCC TGCCCTCGGN TACCTTTCGG	170

(2) INFORMATION FOR SEQ ID NO:48:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 127 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GATCCGGCGG CACGGGGGGT GCCGGCGGCA GCACCGCTGG CGCTGGCGGC AACGGCGGGG	60
CCGGGGGTGG CGGCGGAACC GGTGGGTTGC TCTTCGGCAA CGGCGGTGCC GGCGGGCACG	120
GGGCCGT	127

(2) INFORMATION FOR SEQ ID NO:49:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 81 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

CGGCGGCAAG GGCGGCACCG CCGGCAACGG GAGCGGCGCG GCCGGCGGCA ACGGCGGCAA	60
CGGCGGCTCC GGCTTCAACG G	81

(2) INFORMATION FOR SEQ ID NO:50:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 149 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

GATCAGGGCT GGCCGGCTCC GGCCAGAAGG GCGGTAACGG AGGAGCTGCC GGATTGTTTG	60
GCAACGGCGG GGCCGGNGGT GCCGGCGCGT CCAACCAAGC CGGTAACGGC GGNGCCGGCG	120
GAAACGGTGG TGCCGGTGGG CTGATCTGG	149

(2) INFORMATION FOR SEQ ID NO:51:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 355 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

CGGCACGAGA TCACACCTAC CGAGTGATCG AGATCGTCGG GACCTCGCCC GACGGTGTCG	60
ACGCGGNAAT CCAGGGCGGT CTGGCCCGAG CTGCGCAGAC CATGCGCGCG CTGGACTGGT	120
TCGAAGTACA GTCAATTCGA GGCCACCTGG TCGACGGAGC GGTGCGGCAC TTCCAGGTGA	180
CTATGAAAGT CGGCTTCCGC CTGGAGGATT CCTGAACCTT CAAGCGCGGC CGATAACTGA	240
GGTGCATCAT TAAGCGACTT TTCCAGAACA TCCTGACGCG CTCGAAACGC GGTTCAGCCG	300
ACGGTGGCTC CGCCGAGGCG CTGCCTCCAA AATCCCTGCG ACAATTCGTC GGCGG	355

## (2) INFORMATION FOR SEQ ID NO:52:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 999 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

ATGCATCACC ATCACCATCA CATGCATCAG GTGGACCCCA ACTTGACACG TCGCAAGGGA	60
CGATTGGCGG CACTGGCTAT CGCGGCGATG GCCAGCGCCA GCCTGGTGAC CGTTGCGGTG	120
CCCGCGACCG CCAACGCCGA TCCGGAGCCA GCGCCCCCGG TACCCACAAC GGCCGCCTCG	180
CCGCCGTGCA CCGCTGCAGC GCCACCCGCA CCGGCGACAC CTGTTGCCCC CCCACCACCG	240
GCCGCCGCCA ACACGCCGAA TGCCCAGCCG GGCGATCCCA ACGCAGCACC TCCGCCGGCC	300
GACCCGAACG CACCGCCGCC ACCTGTCATT GCCCCAAACG CACCCCAACC TGTCCGGATC	360
GACAACCCGG TTGGAGGATT CAGCTTCGCG CTGCCTGCTG GCTGGGTGGA GTCTGACGCC	420

GCCCACTTCG ACTACGGTTC AGCACTCCTC AGCAAAACCA CCGGGGACCC GCCATTTCCC	480
GGACAGCCGC CGCCGGTGGC CAATGACACC CGTATCGTGC TCGGCCGGCT AGACCAAAAG	540
CTTTACGCCA GCGCCGAAGC CACCGACTCC AAGGCCGCGG CCCGGTTGGG CTCGGACATG	600
GGTGAGTTCT ATATGCCCTA CCCGGGCACC CGGATCAACC AGGAAACCGT CTCGCTCGAC	660
GCCAACGGGG TGTCTGGAAG CGCGTCGTAT TACGAAGTCA AGTTCAGCGA TCCGAGTAAG	720
CCGAACGGCC AGATCTGGAC GGGCGTAATC GGCTCGCCCG CGGCGAACGC ACCGGACGCC	780
GGGCCCCCTC AGCGCTGGTT TGTGGTATGG CTCGGGACCG CCAACAACCC GGTGGACAAG	840
GGCGCGGCCA AGGCGCTGGC CGAATCGATC CGGCCTTTGG TCGCCCCGCC GCCGGCGCCG	900
GCACCGGCTC CTGCAGAGCC CGCTCCGGCG CCGGCGCCGG CCGGGGAAGT CGCTCCTACC	960
CCGACGACAC CGACACCGCA GCGGACCTTA CCGGCCTGA	999

## (2) INFORMATION FOR SEQ ID NO:53:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 332 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Met	His	His	His	His	His	His	Met	His	Gln	Val	Asp	Pro	Asn	Leu	Thr
1				5					10					15	
Arg	Arg	Lys	Gly	Arg	Leu	Ala	Ala	Leu	Ala	Ile	Ala	Ala	Met	Ala	Ser
			20					25					30		
Ala	Ser	Leu	Val	Thr	Val	Ala	Val	Pro	Ala	Thr	Ala	Asn	Ala	Asp	Pro
		35					40					45			
Glu	Pro	Ala	Pro	Pro	Val	Pro	Thr	Thr	Ala	Ala	Ser	Pro	Pro	Ser	Thr
	50					55					60				

88

Ala Ala Ala Pro Pro Ala Pro Ala Thr Pro Val Ala Pro Pro Pro Pro  
 65 70 75 80  
 Ala Ala<sup>-</sup> Ala Asn Thr Pro Asn Ala Gln Pro Gly Asp Pro Asn Ala Ala  
 85 90 95  
 Pro Pro Pro Ala Asp Pro Asn Ala Pro Pro Pro Pro Val Ile Ala Pro  
 100 105 110  
 Asn Ala Pro Gln Pro Val Arg Ile Asp Asn Pro Val Gly Gly Phe Ser  
 115 120 125  
 Phe Ala Leu Pro Ala Gly Trp Val Glu Ser Asp Ala Ala His Phe Asp  
 130 135 140  
 Tyr Gly Ser Ala Leu Leu Ser Lys Thr Thr Gly Asp Pro Pro Phe Pro  
 145 150 155 160  
 Gly Gln Pro Pro Pro Val Ala Asn Asp Thr Arg Ile Val Leu Gly Arg  
 165 170 175  
 Leu Asp Gln Lys Leu Tyr Ala Ser Ala Glu Ala Thr Asp Ser Lys Ala  
 180 185 190  
 Ala Ala Arg Leu Gly Ser Asp Met Gly Glu Phe Tyr Met Pro Tyr Pro  
 195 200 205  
 Gly Thr Arg Ile Asn Gln Glu Thr Val Ser Leu Asp Ala Asn Gly Val  
 210 215 220  
 Ser Gly Ser Ala Ser Tyr Tyr Glu Val Lys Phe Ser Asp Pro Ser Lys  
 225 230 235 240  
 Pro Asn Gly Gln Ile Trp Thr Gly Val Ile Gly Ser Pro Ala Ala Asn  
 245 250 255  
 Ala Pro Asp Ala Gly Pro Pro Gln Arg Trp Phe Val Val Trp Leu Gly  
 260 265 270  
 Thr Ala Asn Asn Pro Val Asp Lys Gly Ala Ala Lys Ala Leu Ala Glu  
 275 280 285  
 Ser Ile Arg Pro Leu Val Ala Pro Pro Pro Ala Pro Ala Pro Ala Pro  
 290 295 300

Ala Glu Pro Ala Pro Ala Pro Ala Pro Ala Gly Glu Val Ala Pro Thr  
 305 310 315 320

Pro Thr Thr Pro Thr Pro Gln Arg Thr Leu Pro Ala  
 325 330

(2) INFORMATION FOR SEQ ID NO:54:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 20 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Asp Pro Val Asp Ala Val Ile Asn Thr Thr Xaa Asn Tyr Gly Gln Val  
 1 5 10 15  
 Val Ala Ala Leu  
 20

(2) INFORMATION FOR SEQ ID NO:55:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 15 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Ala Val Glu Ser Gly Met Leu Ala Leu Gly Thr Pro Ala Pro Ser  
 1 5 10 15

(2) INFORMATION FOR SEQ ID NO:56:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 19 amino acids  
    (B) TYPE: amino acid  
    (C) STRANDEDNESS:  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Ala	Ala	Met	Lys	Pro	Arg	Thr	Gly	Asp	Gly	Pro	Leu	Glu	Ala	Ala	Lys
1				5					10					15	

Glu Gly Arg

(2) INFORMATION FOR SEQ ID NO:57:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 15 amino acids  
    (B) TYPE: amino acid  
    (C) STRANDEDNESS:  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

Tyr	Tyr	Trp	Cys	Pro	Gly	Gln	Pro	Phe	Asp	Pro	Ala	Trp	Gly	Pro
1				5					10				15	

(2) INFORMATION FOR SEQ ID NO:58:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 14 amino acids  
    (B) TYPE: amino acid  
    (C) STRANDEDNESS:  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

Asp	Ile	Gly	Ser	Glu	Ser	Thr	Glu	Asp	Gln	Gln	Xaa	Ala	Val
1				5					10				

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 13 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

Ala	Glu	Glu	Ser	Ile	Ser	Thr	Xaa	Glu	Xaa	Ile	Val	Pro
1				5					10			

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Asp	Pro	Glu	Pro	Ala	Pro	Pro	Val	Pro	Thr	Ala	Ala	Ala	Ala	Pro	Pro
1				5					10					15	

Ala

## (2) INFORMATION FOR SEQ ID NO:61:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 15 amino acids  
    (B) TYPE: amino acid  
    (C) STRANDEDNESS:  
    (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

Ala	Pro	Lys	Thr	Tyr	Xaa	Glu	Glu	Leu	Lys	Gly	Thr	Asp	Thr	Gly
1				5					10					15

## (2) INFORMATION FOR SEQ ID NO:62:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 30 amino acids  
    (B) TYPE: amino acid  
    (C) STRANDEDNESS:  
    (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Asp	Pro	Ala	Ser	Ala	Pro	Asp	Val	Pro	Thr	Ala	Ala	Gln	Gln	Thr	Ser
1				5					10					15	
Leu	Leu	Asn	Asn	Leu	Ala	Asp	Pro	Asp	Val	Ser	Phe	Ala	Asp		
			20					25					30		

## (2) INFORMATION FOR SEQ ID NO:63:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 187 amino acids  
    (B) TYPE: amino acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

Thr	Gly	Ser	Leu	Asn	Gln	Thr	His	Asn	Arg	Arg	Ala	Asn	Glu	Arg	Lys
1				5				10					15		
Asn	Thr	Thr	Met	Lys	Met	Val	Lys	Ser	Ile	Ala	Ala	Gly	Leu	Thr	Ala
			20				25						30		
Ala	Ala	Ala	Ile	Gly	Ala	Ala	Ala	Gly	Val	Thr	Ser	Ile	Met	Ala	
		35				40					45				
Gly	Gly	Pro	Val	Val	Tyr	Gln	Met	Gln	Pro	Val	Val	Phe	Gly	Ala	Pro
	50					55					60				
Leu	Pro	Leu	Asp	Pro	Ala	Ser	Ala	Pro	Asp	Val	Pro	Thr	Ala	Ala	Gln
65					70				75						80
Leu	Thr	Ser	Leu	Leu	Asn	Ser	Leu	Ala	Asp	Pro	Asn	Val	Ser	Phe	Ala
			85					90					95		
Asn	Lys	Gly	Ser	Leu	Val	Glu	Gly	Gly	Ile	Gly	Gly	Thr	Glu	Ala	Arg
			100					105					110		
Ile	Ala	Asp	His	Lys	Leu	Lys	Lys	Ala	Ala	Glu	His	Gly	Asp	Leu	Pro
		115					120					125			
Leu	Ser	Phe	Ser	Val	Thr	Asn	Ile	Gln	Pro	Ala	Ala	Ala	Gly	Ser	Ala
	130					135					140				
Thr	Ala	Asp	Val	Ser	Val	Ser	Gly	Pro	Lys	Leu	Ser	Ser	Pro	Val	Thr
145					150					155					160
Gln	Asn	Val	Thr	Phe	Val	Asn	Gln	Gly	Gly	Trp	Met	Leu	Ser	Arg	Ala
				165					170					175	
Ser	Ala	Met	Glu	Leu	Leu	Gln	Ala	Ala	Gly	Xaa					
			180						185						

## (2) INFORMATION FOR SEQ ID NO:64:

## (i) SEQUENCE CHARACTERISTICS:

94

- (A) LENGTH: 148 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

```

Asp Glu Val Thr Val Glu Thr Thr Ser Val Phe Arg Ala Asp Phe Leu
1              5              10              15

Ser Glu Leu Asp Ala Pro Ala Gln Ala Gly Thr Glu Ser Ala Val Ser
              20              25              30

Gly Val Glu Gly Leu Pro Pro Gly Ser Ala Leu Leu Val Val Lys Arg
              35              40              45

Gly Pro Asn Ala Gly Ser Arg Phe Leu Leu Asp Gln Ala Ile Thr Ser
              50              55              60

Ala Gly Arg His Pro Asp Ser Asp Ile Phe Leu Asp Asp Val Thr Val
65              70              75              80

Ser Arg Arg His Ala Glu Phe Arg Leu Glu Asn Asn Glu Phe Asn Val
              85              90              95

Val Asp Val Gly Ser Leu Asn Gly Thr Tyr Val Asn Arg Glu Pro Val
              100             105             110

Asp Ser Ala Val Leu Ala Asn Gly Asp Glu Val Gln Ile Gly Lys Leu
              115             120             125

Arg Leu Val Phe Leu Thr Gly Pro Lys Gln Gly Glu Asp Asp Gly Ser
              130             135             140

Thr Gly Gly Pro
145

```

## (2) INFORMATION FOR SEQ ID NO:65:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 230 amino acids

95

(B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

```

Thr Ser Asn Arg Pro Ala Arg Arg Gly Arg Arg Ala Pro Arg Asp Thr
1           5           10           15
Gly Pro Asp Arg Ser Ala Ser Leu Ser Leu Val Arg His Arg Arg Gln
          20           25           30
Gln Arg Asp Ala Leu Cys Leu Ser Ser Thr Gln Ile Ser Arg Gln Ser
          35           40           45
Asn Leu Pro Pro Ala Ala Gly Gly Ala Ala Asn Tyr Ser Arg Arg Asn
          50           55           60
Phe Asp Val Arg Ile Lys Ile Phe Met Leu Val Thr Ala Val Val Leu
65           70           75           80
Leu Cys Cys Ser Gly Val Ala Thr Ala Ala Pro Lys Thr Tyr Cys Glu
          85           90           95
Glu Leu Lys Gly Thr Asp Thr Gly Gln Ala Cys Gln Ile Gln Met Ser
          100          105          110
Asp Pro Ala Tyr Asn Ile Asn Ile Ser Leu Pro Ser Tyr Tyr Pro Asp
          115          120          125
Gln Lys Ser Leu Glu Asn Tyr Ile Ala Gln Thr Arg Asp Lys Phe Leu
          130          135          140
Ser Ala Ala Thr Ser Ser Thr Pro Arg Glu Ala Pro Tyr Glu Leu Asn
145          150          155          160
Ile Thr Ser Ala Thr Tyr Gln Ser Ala Ile Pro Pro Arg Gly Thr Gln
          165          170          175
Ala Val Val Leu Xaa Val Tyr His Asn Ala Gly Gly Thr His Pro Thr
          180          185          190

```

Thr Thr Tyr Lys Ala Phe Asp Trp Asp Gln Ala Tyr Arg Lys Pro Ile  
 195 200 205

Thr Tyr<sup>~</sup> Asp Thr Leu Trp Gln Ala Asp Thr Asp Pro Leu Pro Val Val  
 210 215 220

Phe Pro Ile Val Ala Arg  
 225 230

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 132 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe  
 1 5 10 15

Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser  
 20 25 30

Gly Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly  
 35 40 45

Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val  
 50 55 60

Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val  
 65 70 75 80

Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala  
 85 90 95

Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp  
 100 105 110

97

Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu  
 115 120 125

Gly Pro Pro Ala  
 130

## (2) INFORMATION FOR SEQ ID NO:67:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 100 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

Val Pro Leu Arg Ser Pro Ser Met Ser Pro Ser Lys Cys Leu Ala Ala  
 1 5 10 15

Ala Gln Arg Asn Pro Val Ile Arg Arg Arg Arg Leu Ser Asn Pro Pro  
 20 25 30

Pro Arg Lys Tyr Arg Ser Met Pro Ser Pro Ala Thr Ala Ser Ala Gly  
 35 40 45

Met Ala Arg Val Arg Arg Arg Ala Ile Trp Arg Gly Pro Ala Thr Xaa  
 50 55 60

Ser Ala Gly Met Ala Arg Val Arg Arg Trp Xaa Val Met Pro Xaa Val  
 65 70 75 80

Ile Gln Ser Thr Xaa Ile Arg Xaa Xaa Gly Pro Phe Asp Asn Arg Gly  
 85 90 95

Ser Glu Arg Lys  
 100

## (2) INFORMATION FOR SEQ ID NO:68:

## (i) SEQUENCE CHARACTERISTICS:

98

(A) LENGTH: 163 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

```

Met Thr Asp Asp Ile Leu Leu Ile Asp Thr Asp Glu Arg Val Arg Thr
1           5           10           15
Leu Thr Leu Asn Arg Pro Gln Ser Arg Asn Ala Leu Ser Ala Ala Leu
20           25           30
Arg Asp Arg Phe Phe Ala Xaa Leu Xaa Asp Ala Glu Xaa Asp Asp Asp
35           40           45
Ile Asp Val Val Ile Leu Thr Gly Ala Asp Pro Val Phe Cys Ala Gly
50           55           60
Leu Asp Leu Lys Val Ala Gly Arg Ala Asp Arg Ala Ala Gly His Leu
65           70           75           80
Thr Ala Val Gly Gly His Asp Gln Ala Gly Asp Arg Arg Asp Gln Arg
85           90           95
Arg Arg Gly His Arg Arg Ala Arg Thr Gly Ala Val Leu Arg His Pro
100          105          110
Asp Arg Leu Arg Ala Arg Pro Leu Arg Arg His Pro Arg Pro Gly Gly
115          120          125
Ala Ala Ala His Leu Gly Thr Gln Cys Val Leu Ala Ala Lys Gly Arg
130          135          140
His Arg Xaa Gly Pro Val Asp Glu Pro Asp Arg Arg Leu Pro Val Arg
145          150          155          160
Asp Arg Arg

```

(2) INFORMATION FOR SEQ ID NO:69:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 344 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

```

Met Lys Phe Val Asn His Ile Glu Pro Val Ala Pro Arg Arg Ala Gly
 1             5             10             15
Gly Ala Val Ala Glu Val Tyr Ala Glu Ala Arg Arg Glu Phe Gly Arg
 20             25             30
Leu Pro Glu Pro Leu Ala Met Leu Ser Pro Asp Glu Gly Leu Leu Thr
 35             40             45
Ala Gly Trp Ala Thr Leu Arg Glu Thr Leu Leu Val Gly Gln Val Pro
 50             55             60
Arg Gly Arg Lys Glu Ala Val Ala Ala Ala Val Ala Ala Ser Leu Arg
 65             70             75             80
Cys Pro Trp Cys Val Asp Ala His Thr Thr Met Leu Tyr Ala Ala Gly
 85             90             95
Gln Thr Asp Thr Ala Ala Ala Ile Leu Ala Gly Thr Ala Pro Ala Ala
100            105            110
Gly Asp Pro Asn Ala Pro Tyr Val Ala Trp Ala Ala Gly Thr Gly Thr
115            120            125
Pro Ala Gly Pro Pro Ala Pro Phe Gly Pro Asp Val Ala Ala Glu Tyr
130            135            140
Leu Gly Thr Ala Val Gln Phe His Phe Ile Ala Arg Leu Val Leu Val
145            150            155            160
Leu Leu Asp Glu Thr Phe Leu Pro Gly Gly Pro Arg Ala Gln Gln Leu
165            170            175

```

100

Met Arg Arg Ala Gly Gly Leu Val Phe Ala Arg Lys Val Arg Ala Glu  
 180 185 190  
 His Arg Pro Gly Arg Ser Thr Arg Arg Leu Glu Pro Arg Thr Leu Pro  
 195 200 205  
 Asp Asp Leu Ala Trp Ala Thr Pro Ser Glu Pro Ile Ala Thr Ala Phe  
 210 215 220  
 Ala Ala Leu Ser His His Leu Asp Thr Ala Pro His Leu Pro Pro Pro  
 225 230 235 240  
 Thr Arg Gln Val Val Arg Arg Val Val Gly Ser Trp His Gly Glu Pro  
 245 250 255  
 Met Pro Met Ser Ser Arg Trp Thr Asn Glu His Thr Ala Glu Leu Pro  
 260 265 270  
 Ala Asp Leu His Ala Pro Thr Arg Leu Ala Leu Leu Thr Gly Leu Ala  
 275 280 285  
 Pro His Gln Val Thr Asp Asp Asp Val Ala Ala Ala Arg Ser Leu Leu  
 290 295 300  
 Asp Thr Asp Ala Ala Leu Val Gly Ala Leu Ala Trp Ala Ala Phe Thr  
 305 310 315 320  
 Ala Ala Arg Arg Ile Gly Thr Trp Ile Gly Ala Ala Ala Glu Gly Gln  
 325 330 335  
 Val Ser Arg Gln Asn Pro Thr Gly  
 340

## (2) INFORMATION FOR SEQ ID NO:70:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 485 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

101

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

Asp Asp Pro Asp Met Pro Gly Thr Val Ala Lys Ala Val Ala Asp Ala  
 1 5 10 15  
 Leu Gly Arg Gly Ile Ala Pro Val Glu Asp Ile Gln Asp Cys Val Glu  
 20 25 30  
 Ala Arg Leu Gly Glu Ala Gly Leu Asp Asp Val Ala Arg Val Tyr Ile  
 35 40 45  
 Ile Tyr Arg Gln Arg Arg Ala Glu Leu Arg Thr Ala Lys Ala Leu Leu  
 50 55 60  
 Gly Val Arg Asp Glu Leu Lys Leu Ser Leu Ala Ala Val Thr Val Leu  
 65 70 75 80  
 Arg Glu Arg Tyr Leu Leu His Asp Glu Gln Gly Arg Pro Ala Glu Ser  
 85 90 95  
 Thr Gly Glu Leu Met Asp Arg Ser Ala Arg Cys Val Ala Ala Ala Glu  
 100 105 110  
 Asp Gln Tyr Glu Pro Gly Ser Ser Arg Arg Trp Ala Glu Arg Phe Ala  
 115 120 125  
 Thr Leu Leu Arg Asn Leu Glu Phe Leu Pro Asn Ser Pro Thr Leu Met  
 130 135 140  
 Asn Ser Gly Thr Asp Leu Gly Leu Leu Ala Gly Cys Phe Val Leu Pro  
 145 150 155 160  
 Ile Glu Asp Ser Leu Gln Ser Ile Phe Ala Thr Leu Gly Gln Ala Ala  
 165 170 175  
 Glu Leu Gln Arg Ala Gly Gly Gly Thr Gly Tyr Ala Phe Ser His Leu  
 180 185 190  
 Arg Pro Ala Gly Asp Arg Val Ala Ser Thr Gly Gly Thr Ala Ser Gly  
 195 200 205  
 Pro Val Ser Phe Leu Arg Leu Tyr Asp Ser Ala Ala Gly Val Val Ser  
 210 215 220

102

Met Gly Gly Arg Arg Arg Gly Ala Cys Met Ala Val Leu Asp Val Ser  
 225 230 235 240  
 His Pro Asp Ile Cys Asp Phe Val Thr Ala Lys Ala Glu Ser Pro Ser  
 245 250 255  
 Glu Leu Pro His Phe Asn Leu Ser Val Gly Val Thr Asp Ala Phe Leu  
 260 265 270  
 Arg Ala Val Glu Arg Asn Gly Leu His Arg Leu Val Asn Pro Arg Thr  
 275 280 285  
 Gly Lys Ile Val Ala Arg Met Pro Ala Ala Glu Leu Phe Asp Ala Ile  
 290 295 300  
 Cys Lys Ala Ala His Ala Gly Gly Asp Pro Gly Leu Val Phe Leu Asp  
 305 310 315 320  
 Thr Ile Asn Arg Ala Asn Pro Val Pro Gly Arg Gly Arg Ile Glu Ala  
 325 330 335  
 Thr Asn Pro Cys Gly Glu Val Pro Leu Leu Pro Tyr Glu Ser Cys Asn  
 340 345 350  
 Leu Gly Ser Ile Asn Leu Ala Arg Met Leu Ala Asp Gly Arg Val Asp  
 355 360 365  
 Trp Asp Arg Leu Glu Glu Val Ala Gly Val Ala Val Arg Phe Leu Asp  
 370 375 380  
 Asp Val Ile Asp Val Ser Arg Tyr Pro Phe Pro Glu Leu Gly Glu Ala  
 385 390 395 400  
 Ala Arg Ala Thr Arg Lys Ile Gly Leu Gly Val Met Gly Leu Ala Glu  
 405 410 415  
 Leu Leu Ala Ala Leu Gly Ile Pro Tyr Asp Ser Glu Glu Ala Val Arg  
 420 425 430  
 Leu Ala Thr Arg Leu Met Arg Arg Ile Gln Gln Ala Ala His Thr Ala  
 435 440 445  
 Ser Arg Arg Leu Ala Glu Glu Arg Gly Ala Phe Pro Ala Phe Thr Asp  
 450 455 460

103

Ser Arg Phe Ala Arg Ser Gly Pro Arg Arg Asn Ala Gln Val Thr Ser  
 465 470 475 480

Val Ala Pro Thr Gly  
 485

## (2) INFORMATION FOR SEQ ID NO:71:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 267 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

Gly Val Ile Val Leu Asp Leu Glu Pro Arg Gly Pro Leu Pro Thr Glu  
 1 5 10 15

Ile Tyr Trp Arg Arg Arg Gly Leu Ala Leu Gly Ile Ala Val Val Val  
 20 25 30

Val Gly Ile Ala Val Ala Ile Val Ile Ala Phe Val Asp Ser Ser Ala  
 35 40 45

Gly Ala Lys Pro Val Ser Ala Asp Lys Pro Ala Ser Ala Gln Ser His  
 50 55 60

Pro Gly Ser Pro Ala Pro Gln Ala Pro Gln Pro Ala Gly Gln Thr Glu  
 65 70 75 80

Gly Asn Ala Ala Ala Ala Pro Pro Gln Gly Gln Asn Pro Glu Thr Pro  
 85 90 95

Thr Pro Thr Ala Ala Val Gln Pro Pro Pro Val Leu Lys Glu Gly Asp  
 100 105 110

Asp Cys Pro Asp Ser Thr Leu Ala Val Lys Gly Leu Thr Asn Ala Pro  
 115 120 125

Gln Tyr Tyr Val Gly Asp Gln Pro Lys Phe Thr Met Val Val Thr Asn

104

130	135	140
Ile Gly Leu Val Ser Cys Lys Arg Asp Val Gly Ala Ala Val Leu Ala		
145	150	155 160
Ala Tyr Val Tyr Ser Leu Asp Asn Lys Arg Leu Trp Ser Asn Leu Asp		
	165	170 175
Cys Ala Pro Ser Asn Glu Thr Leu Val Lys Thr Phe Ser Pro Gly Glu		
	180	185 190
Gln Val Thr Thr Ala Val Thr Trp Thr Gly Met Gly Ser Ala Pro Arg		
	195	200 205
Cys Pro Leu Pro Arg Pro Ala Ile Gly Pro Gly Thr Tyr Asn Leu Val		
	210	215 220
Val Gln Leu Gly Asn Leu Arg Ser Leu Pro Val Pro Phe Ile Leu Asn		
225	230	235 240
Gln Pro Pro Pro Pro Pro Gly Pro Val Pro Ala Pro Gly Pro Ala Gln		
	245	250 255
Ala Pro Pro Pro Glu Ser Pro Ala Gln Gly Gly		
	260	265

## (2) INFORMATION FOR SEQ ID NO:72:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 97 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

Leu Ile Ser Thr Gly Lys Ala Ser His Ala Ser Leu Gly Val Gln Val
1 5 10 15
Thr Asn Asp Lys Asp Thr Pro Gly Ala Lys Ile Val Glu Val Val Ala
20 25 30

Gly Gly Ala Ala Ala Asn Ala Gly Val Pro Lys Gly Val Val Val Thr  
35 40 45

Lys Val<sup>+</sup> Asp Asp Arg Pro Ile Asn Ser Ala Asp Ala Leu Val Ala Ala  
50 55 60

Val Arg Ser Lys Ala Pro Gly Ala Thr Val Ala Leu Thr Phe Gln Asp  
65 70 75 80

Pro Ser Gly Gly Ser Arg Thr Val Gln Val Thr Leu Gly Lys Ala Glu  
85 90 95

Gln

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 364 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

Gly Ala Ala Val Ser Leu Leu Ala Ala Gly Thr Leu Val Leu Thr Ala  
1 5 10 15

Cys Gly Gly Gly Thr Asn Ser Ser Ser Ser Gly Ala Gly Gly Thr Ser  
20 25 30

Gly Ser Val His Cys Gly Gly Lys Lys Glu Leu His Ser Ser Gly Ser  
35 40 45

Thr Ala Gln Glu Asn Ala Met Glu Gln Phe Val Tyr Ala Tyr Val Arg  
50 55 60

Ser Cys Pro Gly Tyr Thr Leu Asp Tyr Asn Ala Asn Gly Ser Gly Ala  
65 70 75 80

Gly Val Thr Gln Phe Leu Asn Asn Glu Thr Asp Phe Ala Gly Ser Asp  
85 90 95

Val Pro Leu Asn Pro Ser Thr Gly Gln Pro Asp Arg Ser Ala Glu Arg  
100 105 110

Cys Gly Ser Pro Ala Trp Asp Leu Pro Thr Val Phe Gly Pro Ile Ala  
115 120 125

Ile Thr Tyr Asn Ile Lys Gly Val Ser Thr Leu Asn Leu Asp Gly Pro  
130 135 140

Thr Thr Ala Lys Ile Phe Asn Gly Thr Ile Thr Val Trp Asn Asp Pro  
145 150 155 160

Gln Ile Gln Ala Leu Asn Ser Gly Thr Asp Leu Pro Pro Thr Pro Ile  
165 170 175

Ser Val Ile Phe Arg Ser Asp Lys Ser Gly Thr Ser Asp Asn Phe Gln  
180 185 190

Lys Tyr Leu Asp Gly Val Ser Asn Gly Ala Trp Gly Lys Gly Ala Ser  
195 200 205

Glu Thr Phe Ser Gly Gly Val Gly Val Gly Ala Ser Gly Asn Asn Gly  
210 215 220

Thr Ser Ala Leu Leu Gln Thr Thr Asp Gly Ser Ile Thr Tyr Asn Glu  
225 230 235 240

Trp Ser Phe Ala Val Gly Lys Gln Leu Asn Met Ala Gln Ile Ile Thr  
245 250 255

Ser Ala Gly Pro Asp Pro Val Ala Ile Thr Thr Glu Ser Val Gly Lys  
260 265 270

Thr Ile Ala Gly Ala Lys Ile Met Gly Gln Gly Asn Asp Leu Val Leu  
275 280 285

Asp Thr Ser Ser Phe Tyr Arg Pro Thr Gln Pro Gly Ser Tyr Pro Ile  
290 295 300

Val Leu Ala Thr Tyr Glu Ile Val Cys Ser Lys Tyr Pro Asp Ala Thr  
305 310 315 320

107

Thr Gly Thr Ala Val Arg Ala Phe Met Gln Ala Ala Ile Gly Pro Gly  
325 330 335

Gln Glu Gly Leu Asp Gln Tyr Gly Ser Ile Pro Leu Pro Lys Ser Phe  
340 345 350

Gln Ala Lys Leu Ala Ala Ala Val Asn Ala Ile Ser  
355 360

## (2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 309 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

Gln Ala Ala Ala Gly Arg Ala Val Arg Arg Thr Gly His Ala Glu Asp  
1 5 10 15

Gln Thr His Gln Asp Arg Leu His His Gly Cys Arg Arg Ala Ala Val  
20 25 30

Val Val Arg Gln Asp Arg Ala Ser Val Ser Ala Thr Ser Ala Arg Pro  
35 40 45

Pro Arg Arg His Pro Ala Gln Gly His Arg Arg Arg Val Ala Pro Ser  
50 55 60

Gly Gly Arg Arg Arg Pro His Pro His His Val Gln Pro Asp Asp Arg  
65 70 75 80

Arg Asp Arg Pro Ala Leu Leu Asp Arg Thr Gln Pro Ala Glu His Pro  
85 90 95

Asp Pro His Arg Arg Gly Pro Ala Asp Pro Gly Arg Val Arg Gly Arg  
100 105 110

Gly Arg Leu Arg Arg Val Asp Asp Gly Arg Leu Gln Pro Asp Arg Asp

108

115	120	125
Ala Asp His Gly Ala Pro Val Arg Gly Arg Gly Pro His Arg Gly Val		
130	135	140
Gln His Arg Gly Gly Pro Val Phe Val Arg Arg Val Pro Gly Val Arg		
145	150	155
Cys Ala His Arg Arg Gly His Arg Arg Val Ala Ala Pro Gly Gln Gly		
	165	170
		175
Asp Val Leu Arg Ala Gly Leu Arg Val Glu Arg Leu Arg Pro Val Ala		
	180	185
		190
Ala Val Glu Asn Leu His Arg Gly Ser Gln Arg Ala Asp Gly Arg Val		
	195	200
		205
Phe Arg Pro Ile Arg Arg Gly Ala Arg Leu Pro Ala Arg Arg Ser Arg		
	210	215
		220
Ala Gly Pro Gln Gly Arg Leu His Leu Asp Gly Ala Gly Pro Ser Pro		
	225	230
		235
Leu Pro Ala Arg Ala Gly Gln Gln Gln Pro Ser Ser Ala Gly Gly Arg		
	245	250
		255
Arg Ala Gly Gly Ala Glu Arg Ala Asp Pro Gly Gln Arg Gly Arg His		
	260	265
		270
His Gln Gly Gly His Asp Pro Gly Arg Gln Gly Ala Gln Arg Gly Thr		
	275	280
		285
Ala Gly Val Ala His Ala Ala Ala Gly Pro Arg Arg Ala Ala Val Arg		
	290	295
		300
Asn Arg Pro Arg Arg		
305		

## (2) INFORMATION FOR SEQ ID NO:75:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 580 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

Ser	Ala	Val	Trp	Cys	Leu	Asn	Gly	Phe	Thr	Gly	Arg	His	Arg	His	Gly	1	5	10	15
Arg	Cys	Arg	Val	Arg	Ala	Ser	Gly	Trp	Arg	Ser	Ser	Asn	Arg	Trp	Cys	20	25	30	
Ser	Thr	Thr	Ala	Asp	Cys	Cys	Ala	Ser	Lys	Thr	Pro	Thr	Gln	Ala	Ala	35	40	45	
Ser	Pro	Leu	Glu	Arg	Arg	Phe	Thr	Cys	Cys	Ser	Pro	Ala	Val	Gly	Cys	50	55	60	
Arg	Phe	Arg	Ser	Phe	Pro	Val	Arg	Arg	Leu	Ala	Leu	Gly	Ala	Arg	Thr	65	70	75	80
Ser	Arg	Thr	Leu	Gly	Val	Arg	Arg	Thr	Leu	Ser	Gln	Trp	Asn	Leu	Ser	85	90	95	
Pro	Arg	Ala	Gln	Pro	Ser	Cys	Ala	Val	Thr	Val	Glu	Ser	His	Thr	His	100	105	110	
Ala	Ser	Pro	Arg	Met	Ala	Lys	Leu	Ala	Arg	Val	Val	Gly	Leu	Val	Gln	115	120	125	
Glu	Glu	Gln	Pro	Ser	Asp	Met	Thr	Asn	His	Pro	Arg	Tyr	Ser	Pro	Pro	130	135	140	
Pro	Gln	Gln	Pro	Gly	Thr	Pro	Gly	Tyr	Ala	Gln	Gly	Gln	Gln	Gln	Thr	145	150	155	160
Tyr	Ser	Gln	Gln	Phe	Asp	Trp	Arg	Tyr	Pro	Pro	Ser	Pro	Pro	Pro	Gln	165	170	175	
Pro	Thr	Gln	Tyr	Arg	Gln	Pro	Tyr	Glu	Ala	Leu	Gly	Gly	Thr	Arg	Pro	180	185	190	
Gly	Leu	Ile	Pro	Gly	Val	Ile	Pro	Thr	Met	Thr	Pro	Pro	Pro	Gly	Met	195	200	205	

110

Val Arg Gln Arg Pro Arg Ala Gly Met Leu Ala Ile Gly Ala Val Thr  
 210 215 220  
 Ile Ala Val Val Ser Ala Gly Ile Gly Gly Ala Ala Ala Ser Leu Val  
 225 230 235 240  
 Gly Phe Asn Arg Ala Pro Ala Gly Pro Ser Gly Gly Pro Val Ala Ala  
 245 250 255  
 Ser Ala Ala Pro Ser Ile Pro Ala Ala Asn Met Pro Pro Gly Ser Val  
 260 265 270  
 Glu Gln Val Ala Ala Lys Val Val Pro Ser Val Val Met Leu Glu Thr  
 275 280 285  
 Asp Leu Gly Arg Gln Ser Glu Glu Gly Ser Gly Ile Ile Leu Ser Ala  
 290 295 300  
 Glu Gly Leu Ile Leu Thr Asn Asn His Val Ile Ala Ala Ala Ala Lys  
 305 310 315 320  
 Pro Pro Leu Gly Ser Pro Pro Pro Lys Thr Thr Val Thr Phe Ser Asp  
 325 330 335  
 Gly Arg Thr Ala Pro Phe Thr Val Val Gly Ala Asp Pro Thr Ser Asp  
 340 345 350  
 Ile Ala Val Val Arg Val Gln Gly Val Ser Gly Leu Thr Pro Ile Ser  
 355 360 365  
 Leu Gly Ser Ser Ser Asp Leu Arg Val Gly Gln Pro Val Leu Ala Ile  
 370 375 380  
 Gly Ser Pro Leu Gly Leu Glu Gly Thr Val Thr Thr Gly Ile Val Ser  
 385 390 395 400  
 Ala Leu Asn Arg Pro Val Ser Thr Thr Gly Glu Ala Gly Asn Gln Asn  
 405 410 415  
 Thr Val Leu Asp Ala Ile Gln Thr Asp Ala Ala Ile Asn Pro Gly Asn  
 420 425 430  
 Ser Gly Gly Ala Leu Val Asn Met Asn Ala Gln Leu Val Gly Val Asn  
 435 440 445

111

Ser Ala Ile Ala Thr Leu Gly Ala Asp Ser Ala Asp Ala Gln Ser Gly  
 450 455 460  
 Ser Ile Gly Leu Gly Phe Ala Ile Pro Val Asp Gln Ala Lys Arg Ile  
 465 470 475 480  
 Ala Asp Glu Leu Ile Ser Thr Gly Lys Ala Ser His Ala Ser Leu Gly  
 485 490 495  
 Val Gln Val Thr Asn Asp Lys Asp Thr Pro Gly Ala Lys Ile Val Glu  
 500 505 510  
 Val Val Ala Gly Gly Ala Ala Ala Asn Ala Gly Val Pro Lys Gly Val  
 515 520 525  
 Val Val Thr Lys Val Asp Asp Arg Pro Ile Asn Ser Ala Asp Ala Leu  
 530 535 540  
 Val Ala Ala Val Arg Ser Lys Ala Pro Gly Ala Thr Val Ala Leu Thr  
 545 550 555 560  
 Phe Gln Asp Pro Ser Gly Gly Ser Arg Thr Val Gln Val Thr Leu Gly  
 565 570 575  
 Lys Ala Glu Gln  
 580

## (2) INFORMATION FOR SEQ ID NO:76:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 233 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

Met Asn Asp Gly Lys Arg Ala Val Thr Ser Ala Val Leu Val Val Leu  
 1 5 10 15

112

Gly Ala Cys Leu Ala Leu Trp Leu Ser Gly Cys Ser Ser Pro Lys Pro  
                     20                    25                    30

Asp Ala Glu Glu Gln Gly Val Pro Val Ser Pro Thr Ala Ser Asp Pro  
           35                    40                    45

Ala Leu Leu Ala Glu Ile Arg Gln Ser Leu Asp Ala Thr Lys Gly Leu  
       50                    55                    60

Thr Ser Val His Val Ala Val Arg Thr Thr Gly Lys Val Asp Ser Leu  
 65                    70                    75                    80

Leu Gly Ile Thr Ser Ala Asp Val Asp Val Arg Ala Asn Pro Leu Ala  
                     85                    90                    95

Ala Lys Gly Val Cys Thr Tyr Asn Asp Glu Gln Gly Val Pro Phe Arg  
                     100                    105                    110

Val Gln Gly Asp Asn Ile Ser Val Lys Leu Phe Asp Asp Trp Ser Asn  
           115                    120                    125

Leu Gly Ser Ile Ser Glu Leu Ser Thr Ser Arg Val Leu Asp Pro Ala  
       130                    135                    140

Ala Gly Val Thr Gln Leu Leu Ser Gly Val Thr Asn Leu Gln Ala Gln  
 145                    150                    155                    160

Gly Thr Glu Val Ile Asp Gly Ile Ser Thr Thr Lys Ile Thr Gly Thr  
                     165                    170                    175

Ile Pro Ala Ser Ser Val Lys Met Leu Asp Pro Gly Ala Lys Ser Ala  
           180                    185                    190

Arg Pro Ala Thr Val Trp Ile Ala Gln Asp Gly Ser His His Leu Val  
       195                    200                    205

Arg Ala Ser Ile Asp Leu Gly Ser Gly Ser Ile Gln Leu Thr Gln Ser  
       210                    215                    220

Lys Trp Asn Glu Pro Val Asn Val Asp  
 225                    230

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:

113

- (A) LENGTH: 66 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

```

Val Ile Asp Ile Ile Gly Thr Ser Pro Thr Ser Trp Glu Gln Ala Ala
1           5           10           15
Ala Glu Ala Val Gln Arg Ala Arg Asp Ser Val Asp Asp Ile Arg Val
          20           25           30
Ala Arg Val Ile Glu Gln Asp Met Ala Val Asp Ser Ala Gly Lys Ile
      35           40           45
Thr Tyr Arg Ile Lys Leu Glu Val Ser Phe Lys Met Arg Pro Ala Gln
      50           55           60
Pro Arg
      65
  
```

(2) INFORMATION FOR SEQ ID NO:78:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 69 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

```

Val Pro Pro Ala Pro Pro Leu Pro Pro Leu Pro Pro Ser Pro Ile Ser
1           5           10           15
Cys Ala Ser Pro Pro Ser Pro Pro Leu Pro Pro Ala Pro Pro Val Ala
      20           25           30
  
```

Pro Gly Pro Pro Met Pro Pro Leu Asp Pro Trp Pro Pro Ala Pro Pro  
35 40 45

Leu Pro Tyr Ser Thr Pro Pro Gly Ala Pro Leu Pro Pro Ser Pro Pro  
50 55 60

Ser Pro Pro Leu Pro  
65

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 355 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

Met Ser Asn Ser Arg Arg Arg Ser Leu Arg Trp Ser Trp Leu Leu Ser  
1 5 10 15  
Val Leu Ala Ala Val Gly Leu Gly Leu Ala Thr Ala Pro Ala Gln Ala  
20 25 30  
Ala Pro Pro Ala Leu Ser Gln Asp Arg Phe Ala Asp Phe Pro Ala Leu  
35 40 45  
Pro Leu Asp Pro Ser Ala Met Val Ala Gln Val Ala Pro Gln Val Val  
50 55 60  
Asn Ile Asn Thr Lys Leu Gly Tyr Asn Asn Ala Val Gly Ala Gly Thr  
65 70 75 80  
Gly Ile Val Ile Asp Pro Asn Gly Val Val Leu Thr Asn Asn His Val  
85 90 95  
Ile Ala Gly Ala Thr Asp Ile Asn Ala Phe Ser Val Gly Ser Gly Gln  
100 105 110

115

Thr Tyr Gly Val Asp Val Val Gly Tyr Asp Arg Thr Gln Asp Val Ala  
 115 120 125  
 Val Leu Gln Leu Arg Gly Ala Gly Gly Leu Pro Ser Ala Ala Ile Gly  
 130 135 140  
 Gly Gly Val Ala Val Gly Glu Pro Val Val Ala Met Gly Asn Ser Gly  
 145 150 155 160  
 Gly Gln Gly Gly Thr Pro Arg Ala Val Pro Gly Arg Val Val Ala Leu  
 165 170 175  
 Gly Gln Thr Val Gln Ala Ser Asp Ser Leu Thr Gly Ala Glu Glu Thr  
 180 185 190  
 Leu Asn Gly Leu Ile Gln Phe Asp Ala Ala Ile Gln Pro Gly Asp Ser  
 195 200 205  
 Gly Gly Pro Val Val Asn Gly Leu Gly Gln Val Val Gly Met Asn Thr  
 210 215 220  
 Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe Ala  
 225 230 235 240  
 Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser Gly  
 245 250 255  
 Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly Leu  
 260 265 270  
 Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val Val  
 275 280 285  
 Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val Ile  
 290 295 300  
 Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala Asp  
 305 310 315 320  
 Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp Gln  
 325 330 335  
 Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu Gly  
 340 345 350

Pro Pro Ala  
355

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 205 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

Ser	Pro	Lys	Pro	Asp	Ala	Glu	Glu	Gln	Gly	Val	Pro	Val	Ser	Pro	Thr	1	5	10	15
Ala	Ser	Asp	Pro	Ala	Leu	Leu	Ala	Glu	Ile	Arg	Gln	Ser	Leu	Asp	Ala	20	25	30	
Thr	Lys	Gly	Leu	Thr	Ser	Val	His	Val	Ala	Val	Arg	Thr	Thr	Gly	Lys	35	40	45	
Val	Asp	Ser	Leu	Leu	Gly	Ile	Thr	Ser	Ala	Asp	Val	Asp	Val	Arg	Ala	50	55	60	
Asn	Pro	Leu	Ala	Ala	Lys	Gly	Val	Cys	Thr	Tyr	Asn	Asp	Glu	Gln	Gly	65	70	75	80
Val	Pro	Phe	Arg	Val	Gln	Gly	Asp	Asn	Ile	Ser	Val	Lys	Leu	Phe	Asp	85	90	95	
Asp	Trp	Ser	Asn	Leu	Gly	Ser	Ile	Ser	Glu	Leu	Ser	Thr	Ser	Arg	Val	100	105	110	
Leu	Asp	Pro	Ala	Ala	Gly	Val	Thr	Gln	Leu	Leu	Ser	Gly	Val	Thr	Asn	115	120	125	
Leu	Gln	Ala	Gln	Gly	Thr	Glu	Val	Ile	Asp	Gly	Ile	Ser	Thr	Thr	Lys	130	135	140	
Ile	Thr	Gly	Thr	Ile	Pro	Ala	Ser	Ser	Val	Lys	Met	Leu	Asp	Pro	Gly				

117

145	150	155	160
Ala Lys Ser Ala Arg Pro Ala Thr Val Trp Ile Ala Gln Asp Gly Ser			
	165	170	175
His His Leu Val Arg Ala Ser Ile Asp Leu Gly Ser Gly Ser Ile Gln			
	180	185	190
Leu Thr Gln Ser Lys Trp Asn Glu Pro Val Asn Val Asp			
	195	200	205

## (2) INFORMATION FOR SEQ ID NO:81:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 286 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

Gly Asp Ser Phe Trp Ala Ala Ala Asp Gln Met Ala Arg Gly Phe Val			
1	5	10	15
Leu Gly Ala Thr Ala Gly Arg Thr Thr Leu Thr Gly Glu Gly Leu Gln			
	20	25	30
His Ala Asp Gly His Ser Leu Leu Asp Ala Thr Asn Pro Ala Val			
	35	40	45
Val Ala Tyr Asp Pro Ala Phe Ala Tyr Glu Ile Gly Tyr Ile Xaa Glu			
	50	55	60
Ser Gly Leu Ala Arg Met Cys Gly Glu Asn Pro Glu Asn Ile Phe Phe			
65	70	75	80
Tyr Ile Thr Val Tyr Asn Glu Pro Tyr Val Gln Pro Pro Glu Pro Glu			
	85	90	95
Asn Phe Asp Pro Glu Gly Val Leu Gly Gly Ile Tyr Arg Tyr His Ala			
	100	105	110

118

Ala Thr Glu Gln Arg Thr Asn Lys Xaa Gln Ile Leu Ala Ser Gly Val  
 115 120 125  
 Ala Met Pro Ala Ala Leu Arg Ala Ala Gln Met Leu Ala Ala Glu Trp  
 130 135 140  
 Asp Val Ala Ala Asp Val Trp Ser Val Thr Ser Trp Gly Glu Leu Asn  
 145 150 155 160  
 Arg Asp Gly Val Val Ile Glu Thr Glu Lys Leu Arg His Pro Asp Arg  
 165 170 175  
 Pro Ala Gly Val Pro Tyr Val Thr Arg Ala Leu Glu Asn Ala Arg Gly  
 180 185 190  
 Pro Val Ile Ala Val Ser Asp Trp Met Arg Ala Val Pro Glu Gln Ile  
 195 200 205  
 Arg Pro Trp Val Pro Gly Thr Tyr Leu Thr Leu Gly Thr Asp Gly Phe  
 210 215 220  
 Gly Phe Ser Asp Thr Arg Pro Ala Gly Arg Arg Tyr Phe Asn Thr Asp  
 225 230 235 240  
 Ala Glu Ser Gln Val Gly Arg Gly Phe Gly Arg Gly Trp Pro Gly Arg  
 245 250 255  
 Arg Val Asn Ile Asp Pro Phe Gly Ala Gly Arg Gly Pro Pro Ala Gln  
 260 265 270  
 Leu Pro Gly Phe Asp Glu Gly Gly Gly Leu Arg Pro Xaa Lys  
 275 280 285

## (2) INFORMATION FOR SEQ ID NO:82:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 173 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

119

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

```

Thr Lys Phe His Ala Leu Met Gln Glu Gln Ile His Asn Glu Phe Thr
1           5           10           15
Ala Ala Gln Gln Tyr Val Ala Ile Ala Val Tyr Phe Asp Ser Glu Asp
20           25           30
Leu Pro Gln Leu Ala Lys His Phe Tyr Ser Gln Ala Val Glu Glu Arg
35           40           45
Asn His Ala Met Met Leu Val Gln His Leu Leu Asp Arg Asp Leu Arg
50           55           60
Val Glu Ile Pro Gly Val Asp Thr Val Arg Asn Gln Phe Asp Arg Pro
65           70           75           80
Arg Glu Ala Leu Ala Leu Ala Leu Asp Gln Glu Arg Thr Val Thr Asp
85           90           95
Gln Val Gly Arg Leu Thr Ala Val Ala Arg Asp Glu Gly Asp Phe Leu
100          105          110
Gly Glu Gln Phe Met Gln Trp Phe Leu Gln Glu Gln Ile Glu Glu Val
115          120          125
Ala Leu Met Ala Thr Leu Val Arg Val Ala Asp Arg Ala Gly Ala Asn
130          135          140
Leu Phe Glu Leu Glu Asn Phe Val Ala Arg Glu Val Asp Val Ala Pro
145          150          155          160
Ala Ala Ser Gly Ala Pro His Ala Ala Gly Gly Arg Leu
165          170

```

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 107 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

120

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

```

Arg Ala Asp Glu Arg Lys Asn Thr Thr Met Lys Met Val Lys Ser Ile
1           5           10           15
Ala Ala Gly Leu Thr Ala Ala Ala Ala Ile Gly Ala Ala Ala Ala Gly
20           25           30
Val Thr Ser Ile Met Ala Gly Gly Pro Val Val Tyr Gln Met Gln Pro
35           40           45
Val Val Phe Gly Ala Pro Leu Pro Leu Asp Pro Xaa Ser Ala Pro Xaa
50           55           60
Val Pro Thr Ala Ala Gln Trp Thr Xaa Leu Leu Asn Xaa Leu Xaa Asp
65           70           75           80
Pro Asn Val Ser Phe Xaa Asn Lys Gly Ser Leu Val Glu Gly Gly Ile
85           90           95
Gly Gly Xaa Glu Gly Xaa Xaa Arg Arg Xaa Gln
100          105

```

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 125 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

```

Val Leu Ser Val Pro Val Gly Asp Gly Phe Trp Xaa Arg Val Val Asn
1           5           10           15
Pro Leu Gly Gln Pro Ile Asp Gly Arg Gly Asp Val Asp Ser Asp Thr
20           25           30

```

121

Arg Arg Ala Leu Glu Leu Gln Ala Pro Ser Val Val Xaa Arg Gln Gly  
           35                          40                          45  
 Val Lys Glu Pro Leu Xaa Thr Gly Ile Lys Ala Ile Asp Ala Met Thr  
       50                          55                          60  
 Pro Ile Gly Arg Gly Gln Arg Gln Leu Ile Ile Gly Asp Arg Lys Thr  
   65                          70                          75                          80  
 Gly Lys Asn Arg Arg Leu Cys Arg Thr Pro Ser Ser Asn Gln Arg Glu  
                           85                          90                          95  
 Glu Leu Gly Val Arg Trp Ile Pro Arg Ser Arg Cys Ala Cys Val Tyr  
                   100                          105                          110  
 Val Gly His Arg Ala Arg Arg Gly Thr Tyr His Arg Arg  
           115                          120                          125

## (2) INFORMATION FOR SEQ ID NO:85:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 117 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

Cys Asp Ala Val Met Gly Phe Leu Gly Gly Ala Gly Pro Leu Ala Val  
 1                  5                          10                          15  
 Val Asp Gln Gln Leu Val Thr Arg Val Pro Gln Gly Trp Ser Phe Ala  
                   20                          25                          30  
 Gln Ala Ala Ala Val Pro Val Val Phe Leu Thr Ala Trp Tyr Gly Leu  
           35                          40                          45  
 Ala Asp Leu Ala Glu Ile Lys Ala Gly Glu Ser Val Leu Ile His Ala  
       50                          55                          60  
 Gly Thr Gly Gly Val Gly Met Ala Ala Val Gln Leu Ala Arg Gln Trp

122

65		70		75		80
Gly Val	Glu Val	Phe Val	Thr Ala	Ser Arg	Gly Lys	Trp Asp
		85		90		95
Arg Ala	Xaa Xaa	Phe Asp	Asp Xaa	Pro Tyr	Arg Xaa	Phe Pro
	100		105			110
Arg Ser	Ser Xaa	Gly				
	115					

## (2) INFORMATION FOR SEQ ID NO:86:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 103 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

Met Tyr	Arg Phe	Ala Cys	Arg Thr	Leu Met	Leu Ala	Ala Cys	Ile Leu
1		5		10		15	
Ala Thr	Gly Val	Ala Gly	Leu Gly	Val Gly	Ala Gln	Ser Ala	Ala Gln
	20		25		30		
Thr Ala	Pro Val	Pro Asp	Tyr Tyr	Trp Cys	Pro Gly	Gln Pro	Phe Asp
	35		40		45		
Pro Ala	Trp Gly	Pro Asn	Trp Asp	Pro Tyr	Thr Cys	His Asp	Asp Phe
	50		55		60		
His Arg	Asp Ser	Asp Gly	Pro Asp	His Ser	Arg Asp	Tyr Pro	Gly Pro
65		70		75		80	
Ile Leu	Glu Gly	Pro Val	Leu Asp	Asp Pro	Gly Ala	Ala Pro	Pro Pro
	85		90		95		
Pro Ala	Ala Gly	Gly Gly	Ala				
	100						

## (2) INFORMATION FOR SEQ ID NO:87:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 88 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

```

Val Gln Cys Arg Val Trp Leu Glu Ile Gln Trp Arg Gly Met Leu Gly
1           5           10           15
Ala Asp Gln Ala Arg Ala Gly Gly Pro Ala Arg Ile Trp Arg Glu His
                20           25           30
Ser Met Ala Ala Met Lys Pro Arg Thr Gly Asp Gly Pro Leu Glu Ala
                35           40           45
Thr Lys Glu Gly Arg Gly Ile Val Met Arg Val Pro Leu Glu Gly Gly
50           55           60
Gly Arg Leu Val Val Glu Leu Thr Pro Asp Glu Ala Ala Ala Leu Gly
65           70           75           80
Asp Glu Leu Lys Gly Val Thr Ser
                85

```

## (2) INFORMATION FOR SEQ ID NO:88:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 95 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

124

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

Thr Asp Ala Ala Thr Leu Ala Gln Glu Ala Gly Asn Phe Glu Arg Ile  
 1                                      5                                      10                                      15  
 Ser Gly Asp Leu Lys Thr Gln Ile Asp Gln Val Glu Ser Thr Ala Gly  
                                     20                                      25                                      30  
 Ser Leu Gln Gly Gln Trp Arg Gly Ala Ala Gly Thr Ala Ala Gln Ala  
                                     35                                      40                                      45  
 Ala Val Val Arg Phe Gln Glu Ala Ala Asn Lys Gln Lys Gln Glu Leu  
                                     50                                      55                                      60  
 Asp Glu Ile Ser Thr Asn Ile Arg Gln Ala Gly Val Gln Tyr Ser Arg  
 65                                      70                                      75                                      80  
 Ala Asp Glu Glu Gln Gln Gln Ala Leu Ser Ser Gln Met Gly Phe  
                                     85                                      90                                      95

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 166 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

Met Thr Gln Ser Gln Thr Val Thr Val Asp Gln Gln Glu Ile Leu Asn  
 1                                      5                                      10                                      15  
 Arg Ala Asn Glu Val Glu Ala Pro Met Ala Asp Pro Pro Thr Asp Val  
                                     20                                      25                                      30  
 Pro Ile Thr Pro Cys Glu Leu Thr Xaa Xaa Lys Asn Ala Ala Gln Gln  
                                     35                                      40                                      45  
 Xaa Val Leu Ser Ala Asp Asn Met Arg Glu Tyr Leu Ala Ala Gly Ala  
                                     50                                      55                                      60

125

Lys Glu Arg Gln Arg Leu Ala Thr Ser Leu Arg Asn Ala Ala Lys Xaa  
65 70 75 80

Tyr Gly Glu Val Asp Glu Glu Ala Ala Thr Ala Leu Asp Asn Asp Gly  
85 90 95

Glu Gly Thr Val Gln Ala Glu Ser Ala Gly Ala Val Gly Gly Asp Ser  
100 105 110

Ser Ala Glu Leu Thr Asp Thr Pro Arg Val Ala Thr Ala Gly Glu Pro  
115 120 125

Asn Phe Met Asp Leu Lys Glu Ala Ala Arg Lys Leu Glu Thr Gly Asp  
130 135 140

Gln Gly Ala Ser Leu Ala His Xaa Gly Asp Gly Trp Asn Thr Xaa Thr  
145 150 155 160

Leu Thr Leu Gln Gly Asp  
165

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 5 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

Arg Ala Glu Arg Met  
1 5

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 263 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single

126

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

Val	Ala	Trp	Met	Ser	Val	Thr	Ala	Gly	Gln	Ala	Glu	Leu	Thr	Ala	Ala	1	5	10	15
Gln	Val	Arg	Val	Ala	Ala	Ala	Ala	Tyr	Glu	Thr	Ala	Tyr	Gly	Leu	Thr	20	25	30	
Val	Pro	Pro	Pro	Val	Ile	Ala	Glu	Asn	Arg	Ala	Glu	Leu	Met	Ile	Leu	35	40	45	
Ile	Ala	Thr	Asn	Leu	Leu	Gly	Gln	Asn	Thr	Pro	Ala	Ile	Ala	Val	Asn	50	55	60	
Glu	Ala	Glu	Tyr	Gly	Glu	Met	Trp	Ala	Gln	Asp	Ala	Ala	Ala	Met	Phe	65	70	75	80
Gly	Tyr	Ala	Ala	Ala	Thr	Ala	Thr	Ala	Thr	Ala	Thr	Leu	Leu	Pro	Phe	85	90	95	
Glu	Glu	Ala	Pro	Glu	Met	Thr	Ser	Ala	Gly	Gly	Leu	Leu	Glu	Gln	Ala	100	105	110	
Ala	Ala	Val	Glu	Glu	Ala	Ser	Asp	Thr	Ala	Ala	Ala	Asn	Gln	Leu	Met	115	120	125	
Asn	Asn	Val	Pro	Gln	Ala	Leu	Lys	Gln	Leu	Ala	Gln	Pro	Thr	Gln	Gly	130	135	140	
Thr	Thr	Pro	Ser	Ser	Lys	Leu	Gly	Gly	Leu	Trp	Lys	Thr	Val	Ser	Pro	145	150	155	160
His	Arg	Ser	Pro	Ile	Ser	Asn	Met	Val	Ser	Met	Ala	Asn	Asn	His	Met	165	170	175	
Ser	Met	Thr	Asn	Ser	Gly	Val	Ser	Met	Thr	Asn	Thr	Leu	Ser	Ser	Met	180	185	190	
Leu	Lys	Gly	Phe	Ala	Pro	Ala	Ala	Ala	Ala	Gln	Ala	Val	Gln	Thr	Ala				

127

195						200					205					
Ala	Gln	Asn	Gly	Val	Arg	Ala	Met	Ser	Ser	Leu	Gly	Ser	Ser	Leu	Gly	
210						215					220					
Ser	Ser	Gly	Leu	Gly	Gly	Gly	Val	Ala	Ala	Asn	Leu	Gly	Arg	Ala	Ala	
225						230					235					240
Ser	Val	Arg	Tyr	Gly	His	Arg	Asp	Gly	Gly	Lys	Tyr	Ala	Xaa	Ser	Gly	
245						250					255					
Arg	Arg	Asn	Gly	Gly	Pro	Ala										
260																

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 303 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

```

Met Thr Tyr Ser Pro Gly Asn Pro Gly Tyr Pro Gln Ala Gln Pro Ala
1          5          10          15

Gly Ser Tyr Gly Gly Val Thr Pro Ser Phe Ala His Ala Asp Glu Gly
20          25          30

Ala Ser Lys Leu Pro Met Tyr Leu Asn Ile Ala Val Ala Val Leu Gly
35          40          45

Leu Ala Ala Tyr Phe Ala Ser Phe Gly Pro Met Phe Thr Leu Ser Thr
50          55          60

Glu Leu Gly Gly Gly Asp Gly Ala Val Ser Gly Asp Thr Gly Leu Pro
65          70          75          80

Val Gly Val Ala Leu Leu Ala Ala Leu Leu Ala Gly Val Val Leu Val
85          90          95

```

128

Pro Lys Ala Lys Ser His Val Thr Val Val Ala Val Leu Gly Val Leu  
                   100                                  105                                  110  
 Gly Val Phe Leu Met Val Ser Ala Thr Phe Asn Lys Pro Ser Ala Tyr  
                   115                                  120                                  125  
 Ser Thr Gly Trp Ala Leu Trp Val Val Leu Ala Phe Ile Val Phe Gln  
                   130                                  135                                  140  
 Ala Val Ala Ala Val Leu Ala Leu Leu Val Glu Thr Gly Ala Ile Thr  
                   145                                  150                                  155                                  160  
 Ala Pro Ala Pro Arg Pro Lys Phe Asp Pro Tyr Gly Gln Tyr Gly Arg  
                                   165                                  170                                  175  
 Tyr Gly Gln Tyr Gly Gln Tyr Gly Val Gln Pro Gly Gly Tyr Tyr Gly  
                   180                                  185                                  190  
 Gln Gln Gly Ala Gln Gln Ala Ala Gly Leu Gln Ser Pro Gly Pro Gln  
                   195                                  200                                  205  
 Gln Ser Pro Gln Pro Pro Gly Tyr Gly Ser Gln Tyr Gly Gly Tyr Ser  
                   210                                  215                                  220  
 Ser Ser Pro Ser Gln Ser Gly Ser Gly Tyr Thr Ala Gln Pro Pro Ala  
                   225                                  230                                  235                                  240  
 Gln Pro Pro Ala Gln Ser Gly Ser Gln Gln Ser His Gln Gly Pro Ser  
                   245                                  250                                  255  
 Thr Pro Pro Thr Gly Phe Pro Ser Phe Ser Pro Pro Pro Pro Val Ser  
                   260                                  265                                  270  
 Ala Gly Thr Gly Ser Gln Ala Gly Ser Ala Pro Val Asn Tyr Ser Asn  
                   275                                  280                                  285  
 Pro Ser Gly Gly Glu Gln Ser Ser Ser Pro Gly Gly Ala Pro Val  
                   290                                  295                                  300

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28 amino acids

(B) TYPE: amino acid

129

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

Gly Cys Gly Glu Thr Asp Ala Ala Thr Leu Ala Gln Glu Ala Gly Asn  
1                      5                      10                      15

Phe Glu Arg Ile Ser Gly Asp Leu Lys Thr Gln Ile  
                    20                      25

(2) INFORMATION FOR SEQ ID NO:94:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 16 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

Asp Gln Val Glu Ser Thr Ala Gly Ser Leu Gln Gly Gln Trp Arg Gly  
1                      5                      10                      15

(2) INFORMATION FOR SEQ ID NO:95:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 27 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

130

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

Gly	Cys	Gly	Ser	Thr	Ala	Gly	Ser	Leu	Gln	Gly	Gln	Trp	Arg	Gly	Ala
1				5				10						15	
Ala	Gly	Thr	Ala	Ala	Gln	Ala	Ala	Val	Val	Arg					
			20					25							

(2) INFORMATION FOR SEQ ID NO:96:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 27 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

Gly	Cys	Gly	Gly	Thr	Ala	Ala	Gln	Ala	Ala	Val	Val	Arg	Phe	Gln	Glu
1				5				10						15	
Ala	Ala	Asn	Lys	Gln	Lys	Gln	Glu	Leu	Asp	Glu					
			20					25							

(2) INFORMATION FOR SEQ ID NO:97:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 27 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

Gly	Cys	Gly	Ala	Asn	Lys	Gln	Lys	Gln	Glu	Leu	Asp	Glu	Ile	Ser	Thr
1				5				10					15		

131

Asn Ile Arg Gln Ala Gly Val Gln Tyr Ser Arg  
 20 25

## (2) INFORMATION FOR SEQ ID NO:98:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 28 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

Gly Cys Gly Ile Arg Gln Ala Gly Val Gln Tyr Ser Arg Ala Asp Glu  
 1 5 10 15

Glu Gln Gln Gln Ala Leu Ser Ser Gln Met Gly Phe  
 20 25

## (2) INFORMATION FOR SEQ ID NO:99:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 507 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

ATGAAGATGG TGAAATCGAT CGCCGCAGGT CTGACCGCCG CGGCTGCAAT CGGCGCCGCT	60
GCGGCCGGTG TGAATTCGAT CATGGCTGGC GGCCCGGTG TATACCAGAT GCAGCCGGTC	120
GTCTTCGGCG CGCCACTGCC GTTGGACCCG GCATCCGCCC CTGACGTCCC GACCGCCGCC	180
CAGTTGACCA GCCTGCTCAA CAGCCTCGCC GATCCCAACG TGTCGTTTGC GAACAAGGGC	240

AGTCTGGTCG AGGGCGGCAT CGGGGGCACC GAGGCGCGCA TCGCCGACCA CAAGCTGAAG 300  
 AAGGCCGCCG AGCACGGGGA TCTGCCGCTG TCGTTCAGCG TGACGAACAT CCAGCCGGCG 360  
 GCCGCCGGTT CGGCCACCGC CGACGTTTCC GTCTCGGGTC CGAAGCTCTC GTCGCCGGTC 420  
 ACGCAGAACG TCACGTTCGT GAATCAAGGC GGCTGGATGC TGTCACGCGC ATCGGCGATG 480  
 GAGTTGCTGC AGGCCGCAGG GAACTGA 507

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 168 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

Met Lys Met Val Lys Ser Ile Ala Ala Gly Leu Thr Ala Ala Ala Ala  
 1 5 10 15  
 Ile Gly Ala Ala Ala Ala Gly Val Thr Ser Ile Met Ala Gly Gly Pro  
 20 25 30  
 Val Val Tyr Gln Met Gln Pro Val Val Phe Gly Ala Pro Leu Pro Leu  
 35 40 45  
 Asp Pro Ala Ser Ala Pro Asp Val Pro Thr Ala Ala Gln Leu Thr Ser  
 50 55 60  
 Leu Leu Asn Ser Leu Ala Asp Pro Asn Val Ser Phe Ala Asn Lys Gly  
 65 70 75 80  
 Ser Leu Val Glu Gly Gly Ile Gly Gly Thr Glu Ala Arg Ile Ala Asp  
 85 90 95  
 His Lys Leu Lys Lys Ala Ala Glu His Gly Asp Leu Pro Leu Ser Phe  
 100 105 110

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Ser Val Thr Asn Ile Gln Pro Ala Ala Ala Gly Ser Ala Thr Ala Asp  
 115 120 125

Val Ser Val Ser Gly Pro Lys Leu Ser Ser Pro Val Thr Gln Asn Val  
 130 135 140

Thr Phe Val Asn Gln Gly Gly Trp Met Leu Ser Arg Ala Ser Ala Met  
 145 150 155 160

Glu Leu Leu Gln Ala Ala Gly Asn  
 165

(2) INFORMATION FOR SEQ ID NO:101:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 500 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

CGTGGCAATG TCGTTGACCG TCGGGGCCGG GGTGCGCTCC GCAGATCCCG TGGACGCGGT	60
CATTAACACC ACCTGCAATT ACGGGCAGGT AGTAGCTGCG CTCAACGCGA CGGATCCGGG	120
GGCTGCCGCA CAGTTCAACG CCTCACCAGT GGCAGTCC TATTTGCGCA ATTCCTCGC	180
CGCACCGCCA CCTCAGCGCG CTGCCATGGC CGCGCAATTG CAAGCTGTGC CGGGGGCGGC	240
ACAGTACATC GGCCTTGTCG AGTCGGTTGC CGGCTCCTGC AACAACTATT AAGCCCATGC	300
GGGCCCCATC CCGCGACCCG GCATCGTCGC CGGGGCTAGG CCAGATTGCC CCGCTCCTCA	360
ACGGGGCCGCA TCCGCGACC CGGCATCGTC GCCGGGGCTA GGCCAGATTG CCCCCTCTCT	420
CAACGGGGCCG CATCTCGTGC CGAATTCCTG CAGCCCGGGG GATCCACTAG TTCTAGAGCG	480
GCCGCCACCG CGGTGGAGCT	500



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ATGACAGAGC AGCAGTGGAA TTTCGCGGGT ATCGAGGCCG CGGCAAGCGC AATCCAGGGA 60  
 AATGTCACGT CCATTCATTC CCTCCTTGAC GAGGGGAAGC AGTCCCTGAC CAAGCTCGCA 120  
 GCGGCCTGGG GCGGTAGCGG TTCGGAAGCG TACC 154

## (2) INFORMATION FOR SEQ ID NO:104:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 51 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

Met Thr Glu Gln Gln Trp Asn Phe Ala Gly Ile Glu Ala Ala Ala Ser  
 1 5 10 15  
 Ala Ile Gln Gly Asn Val Thr Ser Ile His Ser Leu Leu Asp Glu Gly  
 20 25 30  
 Lys Gln Ser Leu Thr Lys Leu Ala Ala Ala Trp Gly Gly Ser Gly Ser  
 35 40 45  
 Glu Ala Tyr  
 50

## (2) INFORMATION FOR SEQ ID NO:105:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 282 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

CGGTCGCGCA CTTCCAGGTG ACTATGAAAG TCGGCTTCCG NCTGGAGGAT TCCTGAACCT	60
TCAAGCGCGG CCGATAACTG AGGTGCATCA TTAAGCGACT TTTCCAGAAC ATCCTGACGC	120
GCTCGAAACG CGGCACAGCC GACGGTGGCT CCGNCGAGGC GCTGNCTCCA AAATCCCTGA	180
GACAATTCGN CGGGGGCGCC TACAAGGAAG TCGGTGCTGA ATTCGNCNG TATCTGGTCG	240
ACCTGTGTGG TCTGNAGCCG GACGAAGCGG TGCTCGACGT CG	282

## (2) INFORMATION FOR SEQ ID NO:106:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1565 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

GTATGCGGCC ACTGAAGTCG CCAATGCGGC GGCGGCCAGC TAAGCCAGGA ACAGTCGGCA	60
CGAGAAACCA CGAGAAATAG GGACACGTAA TGGTGGATTT CGGGGCGTTA CCACCGGAGA	120
TCAACTCCGC GAGGATGTAC GCCGGCCCGG GTTCGGCCTC GCTGGTGGCC GCGGCTCAGA	180
TGTGGGACAG CGTGGCGAGT GACCTGTTTT CGGCCGCGTC GGCGTTTCAG TCGGTGGTCT	240
GGGGTCTGAC GGTGGGGTCG TGGATAGGTT CGTCGGCGGG TCTGATGGTG GCGGCGGCCT	300
CGCCGTATGT GGCGTGGATG AGCGTCACCG CGGGGCAGGC CGAGCTGACC GCCGCCAGG	360
TCCGGGTTGC TGCGGCGGCC TACGAGACGG CGTATGGGCT GACGGTGCCC CCGCCGGTGA	420
TCGCCGAGAA CCGTGCTGAA CTGATGATTC TGATAGCGAC CAACCTCTTG GGGCAAACA	480
CCCCGGCGAT CGCGGTCAAC GAGGCCGAAT ACGGCGAGAT GTGGGCCCAA GACGCCGCCG	540
CGATGTTTGG CTACGCCGCG GCGACGGCGA CGGCGACGGC GACGTTGCTG CCGTTCGAGG	600

AGGCGCCGGA GATGACCAGC GCGGGTGGGC TCCTCGAGCA GGCCGCCGCG GTCGAGGAGG	660
CCTCCGACAC CGCCGCGGCG AACCAGTTGA TGAACAATGT GCCCCAGGCG CTGCAACAGC	720
TGGCCCAGCC CACGCAGGGC ACCACGCCTT CTTCCAAGCT GGGTGGCCTG TGGAAAGACGG	780
TCTCGCCGCA TCGGTGCGCG ATCAGCAACA TGGTGTCAAT GGCCAACAAC CACATGTCAA	840
TGACCAACTC GGGTGTGTCA ATGACCAACA CCTTGAGCTC GATGTTGAAG GGCTTTGCTC	900
CGGCGGCGGC CGCCCAGGCC GTGCAAACCG CGGCGCAAAA CGGGGTCCGG GCGATGAGCT	960
CGCTGGGCAG CTCGCTGGGT TCTTCGGGTC TGGGCGGTGG GGTGGCCGCC AACTTGGGTC	1020
GGGCGGCCTC GGTGCGTTCG TTGTCGGTGC CGCAGGCCTG GGCCGCGGCC AACCAGGCAG	1080
TCACCCCGGC GGC GCGGGCG CTGCCGCTGA CCAGCCTGAC CAGCGCCGCG GAAAGAGGGC	1140
CCGGGCAGAT GCTGGGCGGG CTGCCGGTGG GGCAGATGGG CGCCAGGGCC GGTGGTGGGC	1200
TCAGTGGTGT GCTGCGTGTT CCGCCGCGAC CCTATGTGAT GCCGCATTCT CCGGCGGCCG	1260
GCTAGGAGAG GGGGCGCAGA CTGTCGTTAT TTGACCAGTG ATCGGCGGTC TCGGTGTTTC	1320
CGCGGCCGGC TATGACAACA GTCAATGTGC ATGACAAGTT ACAGGTATTA GGTCCAGGTT	1380
CAACAAGGAG ACAGGCAACA TGGCCTCACG TTTTATGACG GATCCGCACG CGATGCGGGA	1440
CATGGCGGGC CGTTTTGAAG TGCACGCCCA GACGGTGGAG GACGAGGCTC GCCGGATGTG	1500
GGCGTCCGCG CAAAACATTT CCGGTGCGGG CTGGAGTGGC ATGGCCGAGG CGACCTCGCT	1560
AGACA	1565

## (2) INFORMATION FOR SEQ ID NO:107:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 391 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

Met	Val	Asp	Phe	Gly	Ala	Leu	Pro	Pro	Glu	Ile	Asn	Ser	Ala	Arg	Met	1	5	10	15
Tyr	Ala	Gly	Pro	Gly	Ser	Ala	Ser	Leu	Val	Ala	Ala	Ala	Gln	Met	Trp	20	25	30	
Asp	Ser	Val	Ala	Ser	Asp	Leu	Phe	Ser	Ala	Ala	Ser	Ala	Phe	Gln	Ser	35	40	45	
Val	Val	Trp	Gly	Leu	Thr	Val	Gly	Ser	Trp	Ile	Gly	Ser	Ser	Ala	Gly	50	55	60	
Leu	Met	Val	Ala	Ala	Ala	Ser	Pro	Tyr	Val	Ala	Trp	Met	Ser	Val	Thr	65	70	75	80
Ala	Gly	Gln	Ala	Glu	Leu	Thr	Ala	Ala	Gln	Val	Arg	Val	Ala	Ala	Ala	85	90	95	
Ala	Tyr	Glu	Thr	Ala	Tyr	Gly	Leu	Thr	Val	Pro	Pro	Pro	Val	Ile	Ala	100	105	110	
Glu	Asn	Arg	Ala	Glu	Leu	Met	Ile	Leu	Ile	Ala	Thr	Asn	Leu	Leu	Gly	115	120	125	
Gln	Asn	Thr	Pro	Ala	Ile	Ala	Val	Asn	Glu	Ala	Glu	Tyr	Gly	Glu	Met	130	135	140	
Trp	Ala	Gln	Asp	Ala	Ala	Ala	Met	Phe	Gly	Tyr	Ala	Ala	Ala	Thr	Ala	145	150	155	160
Thr	Ala	Thr	Ala	Thr	Leu	Leu	Pro	Phe	Glu	Glu	Ala	Pro	Glu	Met	Thr	165	170	175	
Ser	Ala	Gly	Gly	Leu	Leu	Glu	Gln	Ala	Ala	Ala	Val	Glu	Glu	Ala	Ser	180	185	190	
Asp	Thr	Ala	Ala	Ala	Asn	Gln	Leu	Met	Asn	Asn	Val	Pro	Gln	Ala	Leu	195	200	205	
Gln	Gln	Leu	Ala	Gln	Pro	Thr	Gln	Gly	Thr	Thr	Pro	Ser	Ser	Lys	Leu	210	215	220	

Gly Gly Leu Trp Lys Thr Val Ser Pro His Arg Ser Pro Ile Ser Asn  
 225 230 235 240  
 Met Val Ser Met Ala Asn Asn His Met Ser Met Thr Asn Ser Gly Val  
 245 250 255  
 Ser Met Thr Asn Thr Leu Ser Ser Met Leu Lys Gly Phe Ala Pro Ala  
 260 265 270  
 Ala Ala Ala Gln Ala Val Gln Thr Ala Ala Gln Asn Gly Val Arg Ala  
 275 280 285  
 Met Ser Ser Leu Gly Ser Ser Leu Gly Ser Ser Gly Leu Gly Gly Gly  
 290 295 300  
 Val Ala Ala Asn Leu Gly Arg Ala Ala Ser Val Gly Ser Leu Ser Val  
 305 310 315 320  
 Pro Gln Ala Trp Ala Ala Ala Asn Gln Ala Val Thr Pro Ala Ala Arg  
 325 330 335  
 Ala Leu Pro Leu Thr Ser Leu Thr Ser Ala Ala Glu Arg Gly Pro Gly  
 340 345 350  
 Gln Met Leu Gly Gly Leu Pro Val Gly Gln Met Gly Ala Arg Ala Gly  
 355 360 365  
 Gly Gly Leu Ser Gly Val Leu Arg Val Pro Pro Arg Pro Tyr Val Met  
 370 375 380  
 Pro His Ser Pro Ala Ala Gly  
 385 390

## (2) INFORMATION FOR SEQ ID NO:108:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 259 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

ACCAACACCT TGCACTCNAT GTTGAAGGGC TTAGCTCCGG CGGCGGCTCA GGCCGTGGAA	60
ACCGCGGCGG AAAACGGGGT CTGGGCAATG AGCTCGCTGG GCAGCCAGCT GGGTTCGTCTG	120
CTGGGTTCTT CGGGTCTGGG CGCTGGGGTG GCCGCCAACT TGGGTCGGGC GGCCTCGGTC	180
GGTTCGTTGT CGGTGCCGCC AGCATGGGCC GCGGCCAACC AGGCGGTCAC CCCGGCGGCG	240
CGGGCGCTGC CGCTGACCA	259

## (2) INFORMATION FOR SEQ ID NO:109:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 86 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

Thr Asn Thr Leu His Ser Met Leu Lys Gly Leu Ala Pro Ala Ala Ala	1	5	10	15
Gln Ala Val Glu Thr Ala Ala Glu Asn Gly Val Trp Ala Met Ser Ser	20	25	30	
Leu Gly Ser Gln Leu Gly Ser Ser Leu Gly Ser Ser Gly Leu Gly Ala	35	40	45	
Gly Val Ala Ala Asn Leu Gly Arg Ala Ala Ser Val Gly Ser Leu Ser	50	55	60	
Val Pro Pro Ala Trp Ala Ala Ala Asn Gln Ala Val Thr Pro Ala Ala	65	70	75	80
Arg Ala Leu Pro Leu Thr	85			

## (2) INFORMATION FOR SEQ ID NO:110:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1109 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

TACTTGAGAG AATTTGACCT GTTGCCGACG TTGTTTGCTG TCCATCATTG GTGCTAGTTA	60
TGGCCGAGCG GAAGGATTAT CGAAGTGGTG GACTTCGGGG CGTTACCACC GGAGATCAAC	120
TCCGCGAGGA TGTACGCCGG CCCGGGTTCTG GCCTCGCTGG TGGCCGCCGC GAAGATGTGG	180
GACAGCGTGG CGAGTGACCT GTTTTCGGCC GCGTCGGCGT TTCAGTCGGT GGTCTGGGGT	240
CTGACGACGG GATCGTGGAT AGGTTCGTCTG GCGGGTCTGA TGGTGGCGGC GGCCTCGCCG	300
TATGTGGCGT GGATGAGCGT CACCGCGGGG CAGGCCGAGC TGACCGCCGC CCAGGTCCGG	360
GTTGCTGCGG CGGCCTACGA GACGGCGTAT GGGCTGACGG TGCCCCCGCC GGTGATCGCC	420
GAGAACCGTG CTGAACTGAT GATTCTGATA GCGACCAACC TCTTGGGGCA AAACACCCCG	480
GCGATCGCGG TCAACGAGGC CGAATACGGG GAGATGTGGG CCCAAGACGC CGCCGCGATG	540
TTTGGCTACG CCGCCACGGC GGCGACGGCG ACCGAGGCGT TGCTGCCGTT CGAGGACGCC	600
CCACTGATCA CCAACCCCGG CGGGCTCCTT GAGCAGGCCG TCGCGGTCGA GGAGGCCATC	660
GACACCGCCG CGGCGAACCA GTTGATGAAC AATGTGCCCC AAGCGCTGCA ACAACTGGCC	720
CAGCCCACGA AAAGCATCTG GCCGTTCTGAC CAACTGAGTG AACTCTGGAA AGCCATCTCG	780
CCGCATCTGT CGCCGCTCAG CAACATCGTG TCGATGCTCA ACAACCACGT GTCGATGACC	840
AACTCGGGTG TGTCAATGGC CAGCACCTTG CACTCAATGT TGAAGGGCTT TGCTCCGGCG	900
GCGGCTCAGG CCGTGGAAC CGCGGCGCAA AACGGGGTCC AGGCGATGAG CTCGCTGGGC	960

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AGCCAGCTGG GTTCGTCGCT GGGTTCTTCG GGTCTGGGCG CTGGGGTGGC CGCCAACTTG 1020  
 GGTCGGGCGG CCTCGGTCGG TTCGTTGTCG GTGCCGCAGG CCTGGGCCGC GGCCAACCAG 1080  
 GCGGTCACCC CGGCGGCGCG GCGCTGCC 1109

## (2) INFORMATION FOR SEQ ID NO:111:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 341 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

Val Val Asp Phe Gly Ala Leu Pro Pro Glu Ile Asn Ser Ala Arg Met  
 1 5 10 15  
 Tyr Ala Gly Pro Gly Ser Ala Ser Leu Val Ala Ala Ala Lys Met Trp  
 20 25 30  
 Asp Ser Val Ala Ser Asp Leu Phe Ser Ala Ala Ser Ala Phe Gln Ser  
 35 40 45  
 Val Val Trp Gly Leu Thr Thr Gly Ser Trp Ile Gly Ser Ser Ala Gly  
 50 55 60  
 Leu Met Val Ala Ala Ala Ser Pro Tyr Val Ala Trp Met Ser Val Thr  
 65 70 75 80  
 Ala Gly Gln Ala Glu Leu Thr Ala Ala Gln Val Arg Val Ala Ala Ala  
 85 90 95  
 Ala Tyr Glu Thr Ala Tyr Gly Leu Thr Val Pro Pro Pro Val Ile Ala  
 100 105 110  
 Glu Asn Arg Ala Glu Leu Met Ile Leu Ile Ala Thr Asn Leu Leu Gly  
 115 120 125

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Gln Asn Thr Pro Ala Ile Ala Val Asn Glu Ala Glu Tyr Gly Glu Met  
 130 135 140  
 Trp Ala Gln Asp Ala Ala Ala Met Phe Gly Tyr Ala Ala Thr Ala Ala  
 145 150 155 160  
 Thr Ala Thr Glu Ala Leu Leu Pro Phe Glu Asp Ala Pro Leu Ile Thr  
 165 170 175  
 Asn Pro Gly Gly Leu Leu Glu Gln Ala Val Ala Val Glu Glu Ala Ile  
 180 185 190  
 Asp Thr Ala Ala Ala Asn Gln Leu Met Asn Asn Val Pro Gln Ala Leu  
 195 200 205  
 Gln Gln Leu Ala Gln Pro Thr Lys Ser Ile Trp Pro Phe Asp Gln Leu  
 210 215 220  
 Ser Glu Leu Trp Lys Ala Ile Ser Pro His Leu Ser Pro Leu Ser Asn  
 225 230 235 240  
 Ile Val Ser Met Leu Asn Asn His Val Ser Met Thr Asn Ser Gly Val  
 245 250 255  
 Ser Met Ala Ser Thr Leu His Ser Met Leu Lys Gly Phe Ala Pro Ala  
 260 265 270  
 Ala Ala Gln Ala Val Glu Thr Ala Ala Gln Asn Gly Val Gln Ala Met  
 275 280 285  
 Ser Ser Leu Gly Ser Gln Leu Gly Ser Ser Leu Gly Ser Ser Gly Leu  
 290 295 300  
 Gly Ala Gly Val Ala Ala Asn Leu Gly Arg Ala Ala Ser Val Gly Ser  
 305 310 315 320  
 Leu Ser Val Pro Gln Ala Trp Ala Ala Ala Asn Gln Ala Val Thr Pro  
 325 330 335  
 Ala Ala Arg Ala Leu  
 340

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 1256 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

CATCGGAGGG AGTGATCACC ATGCTGTGGC ACGCAATGCC ACCGGAGNTA AATACCGCAC	60
GGCTGATGGC CGGCGCGGGT CCGGCTCCAA TGCTTGCGGC GGCCGCGGGA TGGCAGACGC	120
TTTCGGCGGC TCTGGACGCT CAGGCCGTCG AGTTGACCGC GCGCCTGAAC TCTCTGGGAG	180
AAGCCTGGAC TGGAGGTGGC AGCGACAAGG CGCTTGCGGC TGCAACGCCG ATGGTGGTCT	240
GGCTACAAAC CGCGTCAACA CAGGCCAAGA CCCGTGCGAT GCAGGCGACG GCGCAAGCCG	300
CGGCATACAC CCAGGCCATG GCCACGACGC CGTCGCTGCC GGAGATCGCC GCCAACCACA	360
TCACCCAGGC CGTCCTTACG GCCACCAACT TCTTCGGTAT CAACACGATC CCGATCGCGT	420
TGACCGAGAT GGATTATTTT ATCCGTATGT GGAACCAGGC AGCCCTGGCA ATGGAGGTCT	480
ACCAGGCCGA GACCGCGGTT AACACGCTTT TCGAGAAGCT CGAGCCGATG GCGTCGATCC	540
TTGATCCCGG CGCGAGCCAG AGCACGACGA ACCCGATCTT CGGAATGCCC TCCCCTGGCA	600
GCTCAACACC GGTGCGCCAG TTGCCGCCGG CGGCTACCCA GACCCTCGGC CAACTGGGTG	660
AGATGAGCGG CCCGATGCAG CAGCTGACCC AGCCGCTGCA GCAGGTGACG TCGTTGTTCA	720
GCCAGGTGGG CGGCACCGGC GGC GGCAACC CAGCCGACGA GGAAGCCGCG CAGATGGGCC	780
TGCTCGGCAC CAGTCCGCTG TCGAACCATC CGCTGGCTGG TGGATCAGGC CCCAGCGCGG	840
GCGCGGGCCT GCTGCGCGCG GAGTCGCTAC CTGGCGCAGG TGGGTCGTTG ACCCGCACGC	900
CGCTGATGTC TCAGCTGATC GAAAAGCCGG TTGCCCCCTC GGTGATGCCG GCGGCTGCTG	960
CCGGATCGTC GGCGACGGGT GGC GCCGCTC CGGTGGGTGC GGGAGCGATG GGCCAGGGTG	1020

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CGCAATCCGG CGGCTCCACC AGGCCGGGTC TGGTCGCGCC GGCACCGCTC GCGCAGGAGC	1080
GTGAAGAAGA CGACGAGGAC GACTGGGACG AAGAGGACGA CTGGTGAGCT CCCGTAATGA	1140
CAACAGACTT CCGGCCACC CGGGCCGGA GACTTGCCAA CATTTTGGCG AGGAAGGTAA	1200
AGAGAGAAAG TAGTCCAGCA TGGCAGAGAT GAAGACCGAT GCCGCTACCC TCGCGC	1256

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 432 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

CTAGTGGATG GGACCATGGC CATTTTCTGC AGTCTCACTG CCTTCTGTGT TGACATTTTG	60
GCACGCCGGC GGAAACGAAG CACTGGGGTC GAAGAACGGC TCGCTGCCA TATCGTCCGG	120
AGCTTCCATA CCTTCGTGCG GCCGGAAGAG CTTGTCGTAG TCGGCCGCCA TGACAACCTC	180
TCAGAGTGCG CTCAAACGTA TAAACACGAG AAAGGGCGAG ACCGACGGAA GGTCGAACTC	240
GCCCGATCCC GTGTTTCGCT ATTCTACGCG AACTCGGCGT TGCCCTATGC GAACATCCCA	300
GTGACGTTGC CTTGGGTCGA AGCCATTGCC TGACCGGCTT CGCTGATCGT CCGCGCCAGG	360
TTCTGCAGCG CGTTGTTTCTCAG CTCGGTAGCC GTGGCGTCCC ATTTTGTGCTG GACACCCTGG	420
TACGCCTCCG AA	432

(2) INFORMATION FOR SEQ ID NO:114:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 368 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

Met	Leu	Trp	His	Ala	Met	Pro	Pro	Glu	Xaa	Asn	Thr	Ala	Arg	Leu	Met	1	5	10	15
Ala	Gly	Ala	Gly	Pro	Ala	Pro	Met	Leu	Ala	Ala	Ala	Ala	Gly	Trp	Gln	20	25	30	
Thr	Leu	Ser	Ala	Ala	Leu	Asp	Ala	Gln	Ala	Val	Glu	Leu	Thr	Ala	Arg	35	40	45	
Leu	Asn	Ser	Leu	Gly	Glu	Ala	Trp	Thr	Gly	Gly	Gly	Ser	Asp	Lys	Ala	50	55	60	
Leu	Ala	Ala	Ala	Thr	Pro	Met	Val	Val	Trp	Leu	Gln	Thr	Ala	Ser	Thr	65	70	75	80
Gln	Ala	Lys	Thr	Arg	Ala	Met	Gln	Ala	Thr	Ala	Gln	Ala	Ala	Ala	Tyr	85	90	95	
Thr	Gln	Ala	Met	Ala	Thr	Thr	Pro	Ser	Leu	Pro	Glu	Ile	Ala	Ala	Asn	100	105	110	
His	Ile	Thr	Gln	Ala	Val	Leu	Thr	Ala	Thr	Asn	Phe	Phe	Gly	Ile	Asn	115	120	125	
Thr	Ile	Pro	Ile	Ala	Leu	Thr	Glu	Met	Asp	Tyr	Phe	Ile	Arg	Met	Trp	130	135	140	
Asn	Gln	Ala	Ala	Leu	Ala	Met	Glu	Val	Tyr	Gln	Ala	Glu	Thr	Ala	Val	145	150	155	160
Asn	Thr	Leu	Phe	Glu	Lys	Leu	Glu	Pro	Met	Ala	Ser	Ile	Leu	Asp	Pro	165	170	175	
Gly	Ala	Ser	Gln	Ser	Thr	Thr	Asn	Pro	Ile	Phe	Gly	Met	Pro	Ser	Pro	180	185	190	
Gly	Ser	Ser	Thr	Pro	Val	Gly	Gln	Leu	Pro	Pro	Ala	Ala	Thr	Gln	Thr	195	200	205	

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Leu Gly Gln Leu Gly Glu Met Ser Gly Pro Met Gln Gln Leu Thr Gln  
 210 215 220  
 Pro Leu Gln Gln Val Thr Ser Leu Phe Ser Gln Val Gly Gly Thr Gly  
 225 230 235 240  
 Gly Gly Asn Pro Ala Asp Glu Glu Ala Ala Gln Met Gly Leu Leu Gly  
 245 250 255  
 Thr Ser Pro Leu Ser Asn His Pro Leu Ala Gly Gly Ser Gly Pro Ser  
 260 265 270  
 Ala Gly Ala Gly Leu Leu Arg Ala Glu Ser Leu Pro Gly Ala Gly Gly  
 275 280 285  
 Ser Leu Thr Arg Thr Pro Leu Met Ser Gln Leu Ile Glu Lys Pro Val  
 290 295 300  
 Ala Pro Ser Val Met Pro Ala Ala Ala Ala Gly Ser Ser Ala Thr Gly  
 305 310 315 320  
 Gly Ala Ala Pro Val Gly Ala Gly Ala Met Gly Gln Gly Ala Gln Ser  
 325 330 335  
 Gly Gly Ser Thr Arg Pro Gly Leu Val Ala Pro Ala Pro Leu Ala Gln  
 340 345 350  
 Glu Arg Glu Glu Asp Asp Glu Asp Asp Trp Asp Glu Glu Asp Asp Trp  
 355 360 365

## (2) INFORMATION FOR SEQ ID NO:115:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

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Met Ala Glu Met Lys Thr Asp Ala Ala Thr Leu Ala  
 1                      5                      10

## (2) INFORMATION FOR SEQ ID NO:116:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 396 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

GATCTCCGGC GACCTGAAAA CCCAGATCGA CCAGGTGGAG TCGACGGCAG GTTCGTTGCA	60
GGGCCAGTGG CGCGGCGCGG CGGGGACGGC CGCCCAGGCC GCGGTGGTGC GCTTCCAAGA	120
AGCAGCCAAT AAGCAGAAGC AGGAACTCGA CGAGATCTCG ACGAATATTC GTCAGGCCGG	180
CGTCCAATAC TCGAGGGCCG ACGAGGAGCA GCAGCAGGCG CTGTCCTCGC AAATGGGCTT	240
CTGACCCGCT AATACGAAAA GAAACGGAGC AAAACATGA CAGAGCAGCA GTGGAATTTT	300
GCGGGTATCG AGGCCGCGGC AAGCGCAATC CAGGGAAATG TCACGTCCAT TCATTCCCTC	360
CTTGACGAGG GGAAGCAGTC CCTGACCAAG CTCGCA	396

## (2) INFORMATION FOR SEQ ID NO:117:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 80 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

Ile Ser Gly Asp Leu Lys Thr Gln Ile Asp Gln Val Glu Ser Thr Ala  
 1 5 10 15  
 Gly Ser Leu Gln Gly Gln Trp Arg Gly Ala Ala Gly Thr Ala Ala Gln  
 20 25 30  
 Ala Ala Val Val Arg Phe Gln Glu Ala Ala Asn Lys Gln Lys Gln Glu  
 35 40 45  
 Leu Asp Glu Ile Ser Thr Asn Ile Arg Gln Ala Gly Val Gln Tyr Ser  
 50 55 60  
 Arg Ala Asp Glu Glu Gln Gln Gln Ala Leu Ser Ser Gln Met Gly Phe  
 65 70 75 80

## (2) INFORMATION FOR SEQ ID NO:118:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 387 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

GTGGATCCCG ATCCCGTGTT TCGCTATTCT ACGCGAACTC GGC GTTGCCC TATGCGAACA	60
TCCCAGTGAC GTTGCCCTCG GTCGAAGCCA TTGCCTGACC GGCTTCGCTG ATCGTCCGCG	120
CCAGGTTCTG CAGCGCGTTG TTCAGCTCGG TAGCCGTGGC GTCCCATTTT TGCTGGACAC	180
CCTGGTACGC CTCCGAACCG CTACCGCCCC AGGCCGCTGC GAGCTTGGTC AGGGACTGCT	240
TCCCCTCGTC AAGGAGGGAA TGAATGGACG TGACATTTC CTGGATTGCG CTTGCCGCGG	300
CCTCGATACC CGCGAAATTC CACTGCTGCT CTGTCATGTT TTTGCTCCGT TTCTTTTCGT	360
ATTAGCGGGT CAGAAGCCCA TTTGCGA	387

## (2) INFORMATION FOR SEQ ID NO:119:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 272 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

CGGCACGAGG ATCTCGGTTG GCCCAACGGC GCTGGCGAGG GCTCCGTTCC GGGGGCGAGC	60
TGCGCGCCGG ATGCTTCCTC TGCCCGCAGC CGCGCCTGGA TGGATGGACC AGTTGCTACC	120
TTCCCGACGT TTCGTTGGT GTCTGTGCGA TAGCGGTGAC CCCGGCGCGC ACGTCGGGAG	180
TGTTGGGGGG CAGGCCGGGT CGGTGGTTCG GCCGGGGACG CAGACGGTCT GGACGGAACG	240
GGCGGGGGTT CGCCGATTGG CATCTTTGCC CA	272

## (2) INFORMATION FOR SEQ ID NO:120:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

Asp	Pro	Val	Asp	Ala	Val	Ile	Asn	Thr	Thr	Cys	Asn	Tyr	Gly	Gln	Val
1				5					10					15	
Val Ala Ala Leu															
20															

## (2) INFORMATION FOR SEQ ID NO:121:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 15 amino acids  
    (B) TYPE: amino acid  
    (C) STRANDEDNESS:  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

Ala	Val	Glu	Ser	Gly	Met	Leu	Ala	Leu	Gly	Thr	Pro	Ala	Pro	Ser
1				5					10					15

(2) INFORMATION FOR SEQ ID NO:122:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 19 amino acids  
    (B) TYPE: amino acid  
    (C) STRANDEDNESS:  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

Ala	Ala	Met	Lys	Pro	Arg	Thr	Gly	Asp	Gly	Pro	Leu	Glu	Ala	Ala	Lys
1				5					10					15	

Glu Gly Arg

(2) INFORMATION FOR SEQ ID NO:123:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 15 amino acids  
    (B) TYPE: amino acid  
    (C) STRANDEDNESS:  
    (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

Tyr	Tyr	Trp	Cys	Pro	Gly	Gln	Pro	Phe	Asp	Pro	Ala	Trp	Gly	Pro
1				5					10					15

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

Asp	Ile	Gly	Ser	Glu	Ser	Thr	Glu	Asp	Gln	Gln	Xaa	Ala	Val
1				5					10				

(2) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 13 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

Ala	Glu	Glu	Ser	Ile	Ser	Thr	Xaa	Glu	Xaa	Ile	Val	Pro
1				5					10			

(2) INFORMATION FOR SEQ ID NO:126:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

Asp Pro Glu Pro Ala Pro Pro Val Pro Thr Thr Ala Ala Ser Pro Pro  
1 5 10 15

Ser

(2) INFORMATION FOR SEQ ID NO:127:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 15 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

Ala Pro Lys Thr Tyr Xaa Glu Glu Leu Lys Gly Thr Asp Thr Gly  
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:128:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 30 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

Asp	Pro	Ala	Ser	Ala	Pro	Asp	Val	Pro	Thr	Ala	Ala	Gln	Leu	Thr	Ser
1				5				10					15		
Leu	Leu	Asn	Ser	Leu	Ala	Asp	Pro	Asn	Val	Ser	Phe	Ala	Asn		
		20						25					30		

(2) INFORMATION FOR SEQ ID NO:129:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

Asp	Pro	Pro	Asp	Pro	His	Gln	Xaa	Asp	Met	Thr	Lys	Gly	Tyr	Tyr	Pro
1				5				10					15		
Gly	Gly	Arg	Arg	Xaa	Phe										
		20													

(2) INFORMATION FOR SEQ ID NO:130:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

Asp	Pro	Gly	Tyr	Thr	Pro	Gly
1				5		

## (2) INFORMATION FOR SEQ ID NO:131:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ix) FEATURE:

(D) OTHER INFORMATION: /note= "The Second Residue Can Be Either a Pro or Thr"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

Xaa	Xaa	Gly	Phe	Thr	Gly	Pro	Gln	Phe	Tyr
1				5					10

## (2) INFORMATION FOR SEQ ID NO:132:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 9 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ix) FEATURE:

(D) OTHER INFORMATION: /note= "The Third Residue Can Be Either a Gln or Leu"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

Xaa	Pro	Xaa	Val	Thr	Ala	Tyr	Ala	Gly
1				5				

## (2) INFORMATION FOR SEQ ID NO:133:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 9 amino acids

156

- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

Xaa Xaa Xaa Glu Lys Pro Phe Leu Arg  
1 5

(2) INFORMATION FOR SEQ ID NO:134:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 15 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

Xaa Asp Ser Glu Lys Ser Ala Thr Ile Lys Val Thr Asp Ala Ser  
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:135:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 15 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

Ala Gly Asp Thr Xaa Ile Tyr Ile Val Gly Asn Leu Thr Ala Asp

157

1                      5                      10                      15

## (2) INFORMATION FOR SEQ ID NO:136:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:

Ala Pro Glu Ser Gly Ala Gly Leu Gly Gly Thr Val Gln Ala Gly  
 1                      5                      10                      15

## (2) INFORMATION FOR SEQ ID NO:137:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

Xaa Tyr Ile Ala Tyr Xaa Thr Thr Ala Gly Ile Val Pro Gly Lys Ile  
 1                      5                      10                      15

Asn Val His Leu Val  
 20

Claims

1. A polypeptide comprising an immunogenic portion of a soluble *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen has an N-terminal sequence selected from the group consisting of:

- (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Cys-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu; (SEQ ID No. 120)
- (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser; (SEQ ID No. 121)
- (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg; (SEQ ID No. 122)
- (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro; (SEQ ID No. 123)
- (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val; (SEQ ID No. 124)
- (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro; (SEQ ID No. 125)
- (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Thr-Ala-Ala-Ser-Pro-Pro-Ser; (SEQ ID No. 126)
- (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-Gly; (SEQ ID No. 127)
- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Leu-Thr-Ser-Leu-Leu-Asn-Ser-Leu-Ala-Asp-Pro-Asn-Val-Ser-Phe-Ala-Asn; (SEQ ID No. 128) and
- (j) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 136)

wherein Xaa may be any amino acid.

2. A polypeptide comprising an immunogenic portion of an *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative

substitutions and/or modifications, wherein said antigen has an N-terminal sequence selected from the group consisting of:

- (a) Asp-Pro-Pro-Asp-Pro-His-Gln-Xaa-Asp-Met-Thr-Lys-Gly-Tyr-Tyr-Pro-Gly-Gly-Arg-Arg-Xaa-Phe; (SEQ ID No. 129) and
- (b) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No. 137), wherein Xaa may be any amino acid.

3. A polypeptide comprising an immunogenic portion of a soluble *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos.: 1, 2, 4-10, 13-25, 52, 99 and 101, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 1, 2, 4-10, 13-25, 52, 99 and 101 or a complement thereof under moderately stringent conditions.

4. A polypeptide comprising an immunogenic portion of a *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos.: 26-51, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 26-51 or a complement thereof under moderately stringent conditions.

5. A DNA molecule comprising a nucleotide sequence encoding a polypeptide according to any one of claims 1-4.

6. An expression vector comprising a DNA molecule according to claim 5.

7. A host cell transformed with an expression vector according to claim 6.

8. The host cell of claim 7 wherein the host cell is selected from the group consisting of *E. coli*, yeast and mammalian cells.

9. A pharmaceutical composition comprising one or more polypeptides according to any one of claims 1-4 and a physiologically acceptable carrier.

10. A pharmaceutical composition comprising one or more DNA molecules according to claim 5 and a physiologically acceptable carrier.

11. A pharmaceutical composition comprising one or more DNA sequences recited in SEQ ID Nos.: 3, 11 and 12; and a physiologically acceptable carrier.

12. A vaccine comprising one or more polypeptides according to any one of claims 1-4 and a non-specific immune response enhancer.

13. A vaccine comprising:  
a polypeptide having an N-terminal sequence selected from the group consisting of sequences recited in SEQ ID NO: 134 and 135; and  
a non-specific immune response enhancer.

14. A vaccine comprising:  
one or more polypeptides encoded by a DNA sequence selected from the group consisting of SEQ ID Nos.: 3, 11 and 12, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 3, 11 and 12; and  
a non-specific immune response enhancer.

15. The vaccine of claims 12-14 wherein the non-specific immune response enhancer is an adjuvant.

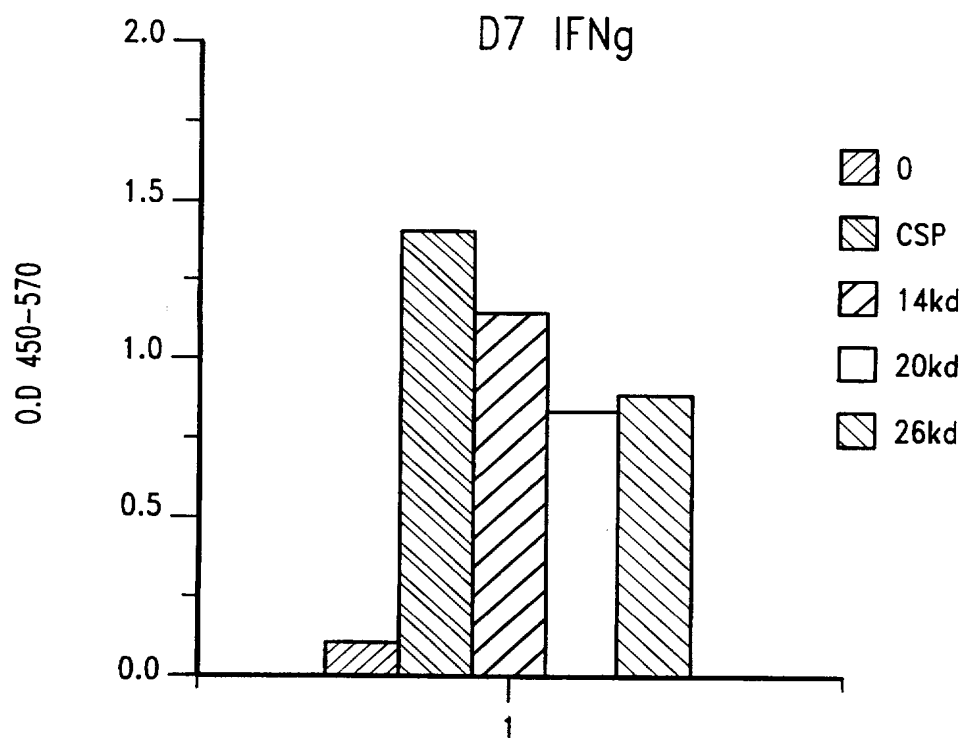
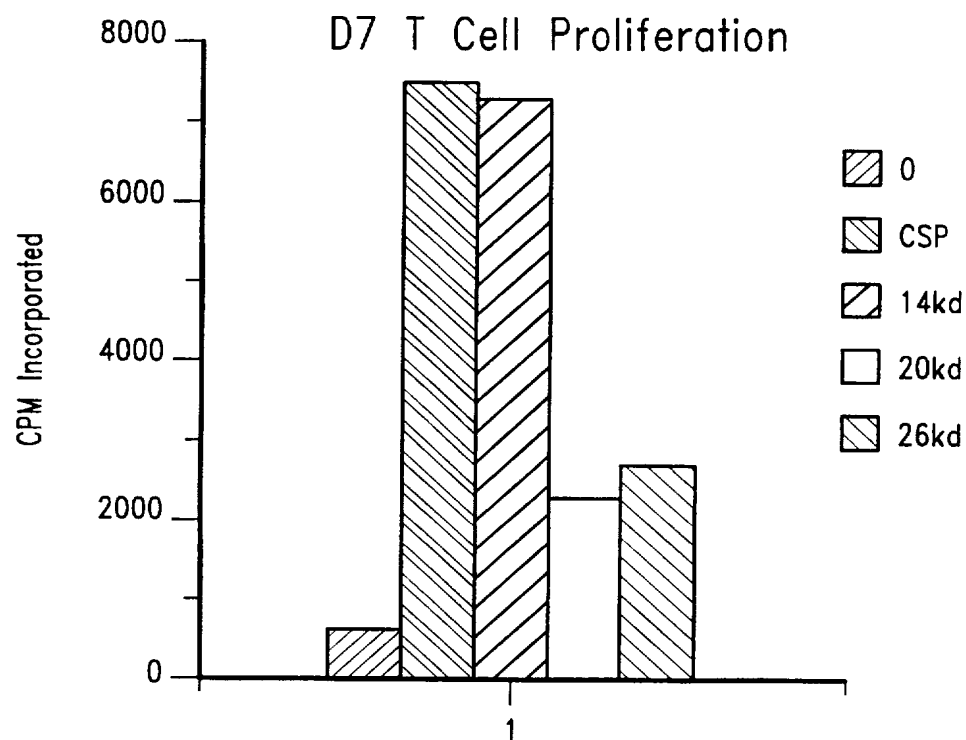
16. A vaccine comprising one or more DNA molecules according to claim 5 and a non-specific immune response enhancer.

17. A vaccine comprising one or more DNA sequences recited in SEQ ID Nos.: 3, 11 and 12; and a non-specific immune response enhancer.
18. The vaccine of claims 16 or 17 wherein the non-specific immune response enhancer is an adjuvant.
19. A method for inducing protective immunity in a patient, comprising administering to a patient a pharmaceutical composition according to any one of claims 9-11.
20. A method for inducing protective immunity in a patient, comprising administering to a patient a vaccine according to any one of claims 12-18.
21. A fusion protein comprising two or more polypeptides according to any one of claims 1-4.
22. A fusion protein comprising one or more polypeptides according to any one of claims 1-4 and ESAT-6.
23. A pharmaceutical composition comprising a fusion protein according to claim 21 or 22 and a physiologically acceptable carrier.
24. A vaccine comprising a fusion protein according to claims 21 or 22 and a non-specific immune response enhancer.
25. The vaccine of claim 24 wherein the non-specific immune response enhancer is an adjuvant.
26. A method for inducing protective immunity in a patient, comprising administering to a patient a pharmaceutical composition according to claim 23.
27. A method for inducing protective immunity in a patient, comprising administering to a patient a vaccine according to claims 24 or 25.

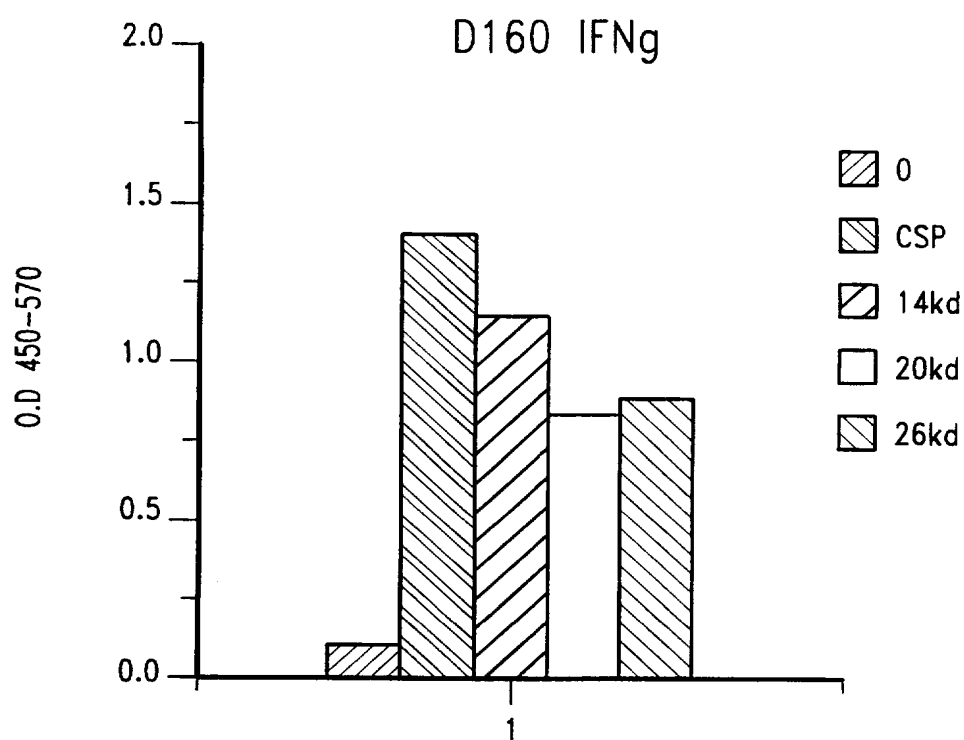
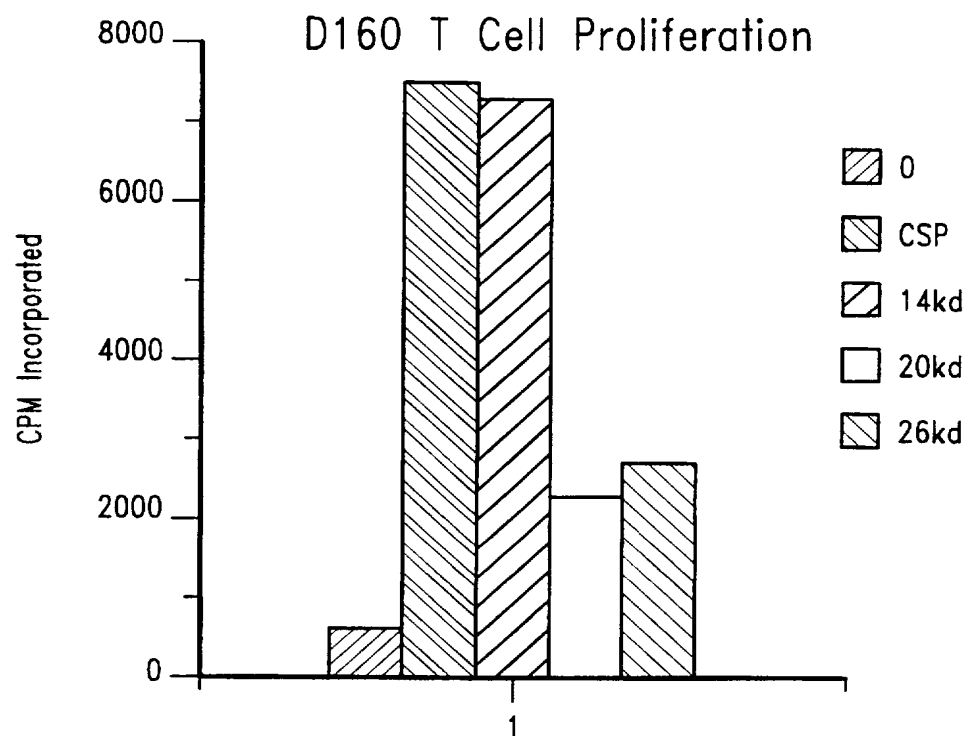
28. A method for detecting tuberculosis in a patient, comprising:
- (a) contacting dermal cells of a patient with one or more polypeptides according to any one of claims 1-4; and
  - (b) detecting an immune response on the patient's skin and therefrom detecting tuberculosis in the patient.
29. A method for detecting tuberculosis in a patient, comprising:
- (a) contacting dermal cells of a patient with a polypeptide having an N-terminal sequence selected from the group consisting of sequences recited in SEQ ID NO: 134 and 135; and
  - (b) detecting an immune response on the patient's skin and therefrom detecting tuberculosis in the patient.
30. A method for detecting tuberculosis in a patient, comprising:
- (a) contacting dermal cells of a patient with one or more polypeptides encoded by a DNA sequence selected from the group consisting of SEQ ID Nos.: 3, 11 and 12, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 3, 11 and 12; and
  - (b) detecting an immune response on the patient's skin and therefrom detecting tuberculosis in the patient.
31. The method of any one of claims 28-30 wherein the immune response is induration.
32. A diagnostic kit comprising:
- (a) a polypeptide according to any one of claims 1-4; and
  - (b) apparatus sufficient to contact said polypeptide with the dermal cells of a patient.

33. A diagnostic kit comprising:
- (a) a polypeptide having an N-terminal sequence selected from the group consisting of sequences recited in SEQ ID NO: 134 and 135; and
  - (b) apparatus sufficient to contact said polypeptide with the dermal cells of a patient.
34. A diagnostic kit comprising:
- (a) a polypeptide encoded by a DNA sequence selected from the group consisting of SEQ ID Nos.: 3, 11 and 12, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 3, 11 and 12; and
  - (b) apparatus sufficient to contact said polypeptide with the dermal cells of a patient.

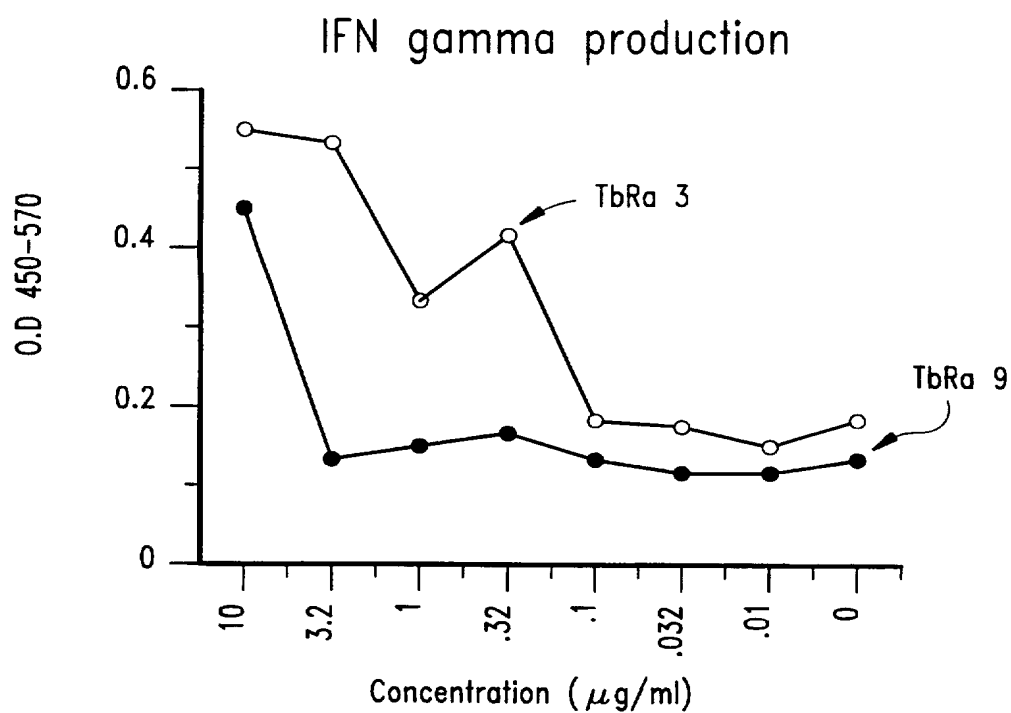
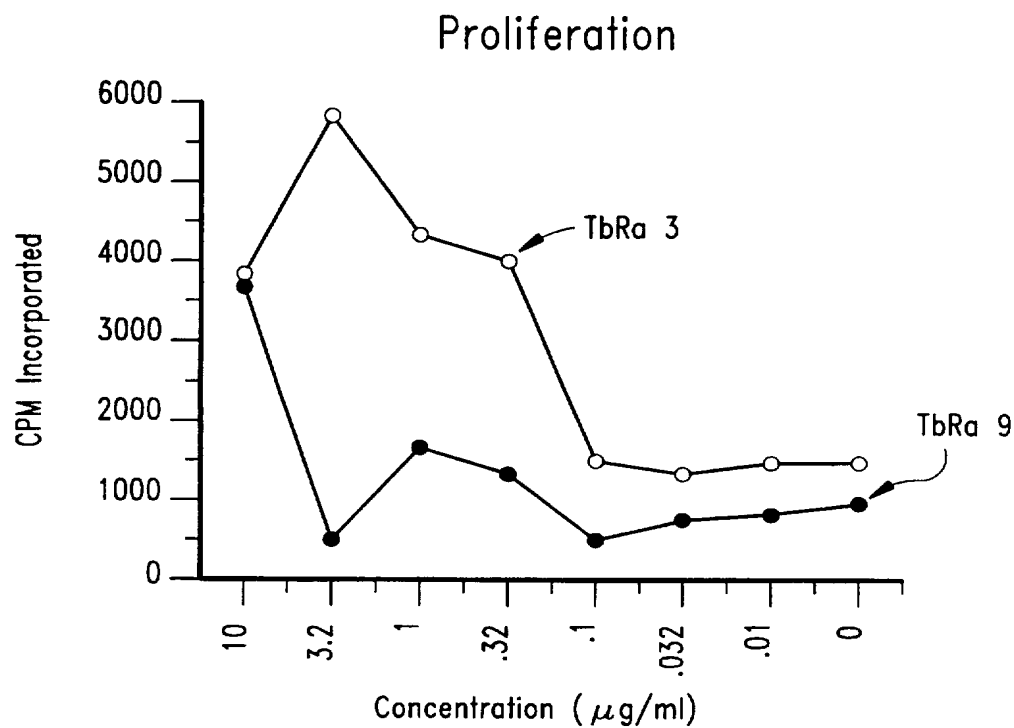
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*Fig. 1A*

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*Fig. 1B*

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*Fig. 2*